



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<p>(51) International Patent Classification ⁶ : A01N 43/08, 43/10, 43/26, 43/40, 43/74, 43/90, A61K 31/445, C07D 211/20, 211/26, 401/04, 401/12, 401/14, 405/04, 405/14, 409/14, 413/14, 417/14, 471/10</p>	<p>A1</p>	<p>(11) International Publication Number: WO 98/10653 (43) International Publication Date: 19 March 1998 (19.03.98)</p>
<p>(21) International Application Number: PCT/US97/16103 (22) International Filing Date: 10 September 1997 (10.09.97) (30) Priority Data: 60/026,054 13 September 1996 (13.09.96) US 9624172.4 19 November 1996 (19.11.96) GB (71) Applicant (for all designated States except US): MERCK & CO., INC. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): NARGUND, Ravi [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US); PATCHETT, Arthur, A. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). TATA, James [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). (74) Common Representative: MERCK & CO., INC.; 126 East Lincoln Avenue, Rahway, NJ 07065 (US).</p>		<p>(81) Designated States: AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, EE, GE, HU, ID, IL, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, SL, TJ, TM, TR, TT, UA, US, UZ, VN, YU, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).</p> <p>Published With international search report.</p>
<p>(54) Title: PIPERIDINES, PYRROLIDINES AND HEXAHYDRO-1H-AZEPINES PROMOTE RELEASE OF GROWTH HORMONE</p>		
<p>(57) Abstract</p> <p>The present invention is directed to certain piperidines, pyrrolidines, and hexahydro-1H-azepines of general structural formula (I) wherein B is selected from (A) and (B) and R¹, R^{1a}, R^{2a}, R^{3a}, R^{3b}, R⁴, R^{4a}, R^{4b}, R⁵, D, E, X, Y, n, x and y are as defined herein. These compounds promote the release of growth hormone in humans and animals. This property can be utilized to promote the growth of food animals to render the production of edible meat products more efficient, and in humans, to treat physiological or medical conditions characterized by a deficiency in growth hormone secretion, such as short stature in growth hormone deficient children, and to treat medical conditions which are improved by the anabolic effects of growth hormone. Growth hormone releasing compositions containing such compounds as the active ingredient thereof are also disclosed.</p> <div style="text-align: center;"> $\begin{array}{c} R^{1a} \quad R^{2a} \quad O \\ \quad \quad \\ R^1 - C - N - C - \left(\begin{array}{c} R^{4a} \\ \\ R^{4b} \end{array} \right)_x - E - \left(\begin{array}{c} R^{4a} \\ \\ R^{4b} \end{array} \right)_y - N \begin{array}{l} R^4 \\ R^5 \end{array} \\ \\ C=O \\ \\ B \end{array} \quad (I)$ </div> <div style="display: flex; justify-content: space-around; align-items: center;"> <div style="text-align: center;"> <p>(B)</p> </div> <div style="text-align: center;"> <p>(A)</p> </div> </div>		

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakhstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

- 1 -

TITLE OF THE INVENTION**PIPERIDINES, PYRROLIDINES AND HEXAHYDRO-1H-AZEPINES PROMOTE RELEASE OF GROWTH HORMONE****5 BACKGROUND OF THE INVENTION**

Growth hormone, which is secreted from the pituitary, stimulates growth of all tissues of the body that are capable of growing. In addition, growth hormone is known to have the following basic effects on the metabolic processes of the body: (1) Increased rate of protein
10 synthesis in all cells of the body; (2) Decreased rate of carbohydrate utilization in cells of the body; (3) Increased mobilization of free fatty acids and use of fatty acids for energy. A deficiency in growth hormone secretion can result in various medical disorders, such as dwarfism.

Various ways are known to release growth hormone. For
15 example, chemicals such as arginine, L-3,4-dihydroxyphenylalanine (L-DOPA), glucagon, vasopressin, and insulin induced hypoglycemia, as well as activities such as sleep and exercise, indirectly cause growth hormone to be released from the pituitary by acting in some fashion on the hypothalamus perhaps either to decrease somatostatin secretion
20 or to increase the secretion of the known secretagogue growth hormone releasing factor (GRF) or an unknown endogenous growth hormone-releasing hormone or all of these.

In cases where increased levels of growth hormone were desired, the problem was generally solved by providing exogenous
25 growth hormone or by administering GRF or a peptidal compound which stimulated growth hormone production and/or release. In either case the peptidyl nature of the compound necessitated that it be administered by injection. Initially the source of growth hormone was the extraction of the pituitary glands of cadavers. This resulted in a
30 very expensive product and carried with it the risk that a disease associated with the source of the pituitary gland could be transmitted to the recipient of the growth hormone. Recombinant growth hormone has become available which, while no longer carrying any risk of disease transmission, is still a very expensive product which

- 2 -

must be given by injection or by a nasal spray. Other compounds have been developed which stimulate the release of endogenous growth hormone such as analogous peptidyl compounds related to GRF or the peptides of U.S. Patent 4,411,890. These peptides, while considerably smaller than growth hormones are still susceptible to various proteases. As with most peptides, their potential for oral bioavailability is low. Non peptidal growth hormone secretagogues are disclosed in e.g., U.S. Patent Nos 5,206,235, 5,283,241, 5,284,841, 5,310,737, 5,317,017, 5,374,721, 5,430,144, 5,434,261, 5,438,136, 5,492,916, 5,494,919, 5,494,920, and 5,536,716. Other growth hormone secretagogues are disclosed e.g., in PCT Patent Publications WO 94/13696, WO 94/19367, WO 95/03289, WO 95/03290, WO 95/09633, WO 95/11029, WO 95/12598, WO 95/13069, WO 95/14666, WO 95/16675, WO 95/16692, WO 95/17422, WO 95/17423, WO 95/34311, WO 96/02530 and WO 96/22997. The instant compounds are low molecular weight peptide analogs for promoting the release of growth hormone which have good stability in a variety of physiological environments and which may be administered parenterally, nasally or by the oral route.

20

SUMMARY OF THE INVENTION

The instant invention is directed to certain piperidines, pyrrolidines, and hexahydro-1H-azepines which have the ability to stimulate the release of natural or endogenous growth hormone. The compounds thus have the ability to be used to treat conditions which require the stimulation of growth hormone production or secretion such as in humans with a deficiency of natural growth hormone or in animals used for food or wool production where the stimulation of growth hormone will result in a larger, more productive animal. Thus, it is an object of the instant invention to describe the piperidine compounds. It is a further object of this invention to describe procedures for the preparation of such compounds. A still further object is to describe the use of such compounds to increase the secretion of growth hormone in humans and animals. A still further object of this invention is to describe

25

30

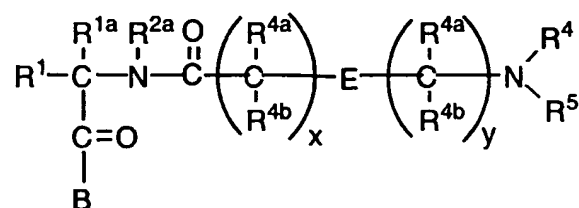
- 3 -

compositions containing the piperidine compounds for the use of treating humans and animals so as to increase the level of growth hormone secretions. Further objects will become apparent from a reading of the following description.

5

DESCRIPTION OF THE INVENTION

The novel piperidines, pyrrolidines, and hexahydro-1H-azepines of the instant invention are described by structural Formula I:



10

Formula I

wherein:

R^1 is selected from the group consisting of:

- 15 C_1 - C_{10} alkyl, -aryl-, aryl (C_1 - C_6 alkyl)-, heteroaryl-, heteroaryl(C_1 - C_6 alkyl)-, (C_3 - C_7 cycloalkyl)-(C_1 - C_6 alkyl)-, (C_1 - C_5 alkyl)-K-(C_1 - C_5 alkyl)-, aryl-(C_0 - C_5 alkyl)-K-(C_1 - C_5 alkyl)-, 20 heteroaryl-(C_0 - C_5 alkyl)-K-(C_1 - C_5 alkyl)-, and (C_3 - C_7 cycloalkyl)-(C_0 - C_5 alkyl)-K-(C_1 - C_5 alkyl)-, wherein K is -O-, -S(O)_m-, -N(R²)C(O)-, -C(O)N(R²)-, -OC(O)-, -C(O)O-, -CR²=CR²- or -C≡C-, wherein R² and the alkyl groups may be further substituted with 1 to 9 25 halo, -S(O)_mR^{2a}, 1 to 3 of -OR^{2a}, or -C(O)OR^{2a}, and wherein aryl is phenyl or naphthyl, and heteroaryl is selected from indolyl, thiophenyl, benzofuranyl, benzothiophenyl, aza-indolyl, pyridinyl, quinolinyl, and benzimidazolyl, wherein aryl and heteroaryl are unsubstituted or substituted with phenyl, phenoxy, halophenyl, 1 to 3 of - C_1 - C_6 alkyl, 1 to 30 3 of halo, 1 to 2 of -OR², methylenedioxy, -S(O)_mR², 1 to 2 of -CF₃, -

- 4 -

OCF₃, nitro, -N(R²)(R²), -N(R²)C(O)(R²), -C(O)OR², -C(O)N(R²)(R²), -SO₂N(R²)(R²), -N(R²)SO₂-aryl, or -N(R²)SO₂R²;

R^{1a} is hydrogen or C₁-C₄ alkyl;

5

R² is selected from the group consisting of:

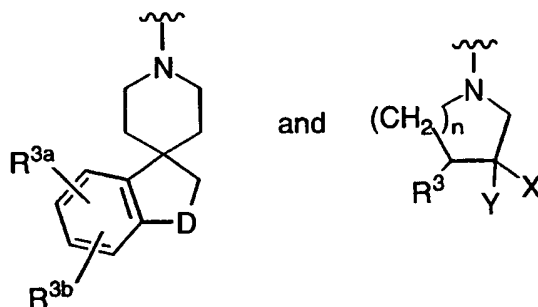
hydrogen, -C₁-C₆ alkyl, -C₃-C₇ cycloalkyl, and -CH₂-phenyl,

wherein the alkyl or the cycloalkyl is unsubstituted or substituted with hydroxyl, C₁-C₃ alkoxy, thioalkyl, C(O)OR^{2a}, and where, if two -C₁-C₆

- 10 alkyl groups are present on one atom, they may be joined to form a C₃-C₈ cyclic ring being selected from the group consisting of pyrrolidine, piperidine, piperazine, morpholine, thiomorpholine, optionally substituted by hydroxyl;

- 15 R^{2a} is hydrogen or C₁-C₆ alkyl;

B is selected from:



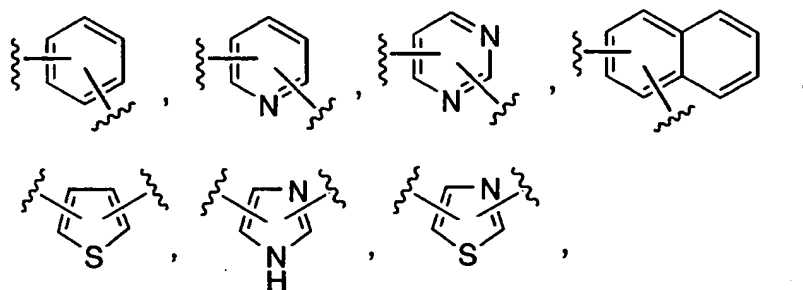
- R³ is selected from: hydrogen, -(CH₂)_rphenyl, -(CH₂)_rpyridyl, -
- 20 (CH₂)_rthienyl, -(CH₂)_rbenzimidazolyl, -(CH₂)_rquinolinyl, -
- (CH₂)_rnaphthyl, -(CH₂)_rindolyl, -C₁-C₁₀ alkyl, -C₃-C₇ cycloalkyl,
- where the phenyl, pyridyl, naphthyl, indolyl, thienyl, benzimidazolyl, quinolinyl, and C₃-C₇ cycloalkyl rings may be substituted by 1 to 3
- substituents selected from the group consisting of: C₁-C₆ alkyl, halogen,
- 25 -OR², -NHSO₂CF₃, -(CH₂)_rOR⁶, -(CH₂)_rN(R²)(R⁶), -(CH₂)_r(R⁶), -
- (CH₂)_rC(O)OR², -(CH₂)_rC(O)OR⁶, -(CH₂)_rOC(O)R², -

- 5 -

- $(\text{CH}_2)_r\text{OC(O)}\text{R}^6$, $-(\text{CH}_2)_r\text{C(O)}\text{R}^2$, $-(\text{CH}_2)_r\text{C(O)}\text{R}^6$, -
 $(\text{CH}_2)_r\text{C(O)}\text{N(R}^2)(\text{R}^2)$, $-(\text{CH}_2)_r\text{C(O)}\text{N(R}^2)(\text{R}^6)$, -
 $(\text{CH}_2)_r\text{N(R}^2)\text{C(O)}(\text{R}^2)$, $-(\text{CH}_2)_r\text{N(R}^2)\text{C(O)}\text{R}^6$ $-(\text{CH}_2)_r\text{N(R}^6)\text{C(O)}\text{R}^2$, -
 $(\text{CH}_2)_r\text{N(R}^6)\text{C(O)}\text{R}^6$, $-(\text{CH}_2)_r\text{N(R}^2)\text{C(O)}\text{OR}^2$, $-(\text{CH}_2)_r\text{N(R}^2)\text{C(O)}\text{OR}^6$,
 5 $-(\text{CH}_2)_r\text{N(R}^6)\text{C(O)}\text{OR}^2$, $-(\text{CH}_2)_r\text{N(R}^6)\text{C(O)}\text{OR}^6$, -
 $(\text{CH}_2)_r\text{N(R}^2)\text{C(O)}\text{N(R}^2)(\text{R}^6)$, $-(\text{CH}_2)_r\text{N(R}^2)\text{C(O)}\text{N(R}^2)(\text{R}^2)$, -
 $(\text{CH}_2)_r\text{N(R}^6)\text{C(O)}\text{N(R}^2)(\text{R}^6)$, $-(\text{CH}_2)_r\text{N(R}^2)\text{SO}_2\text{R}^2$, -
 $(\text{CH}_2)_r\text{N(R}^6)\text{SO}_2\text{R}^2$, $-(\text{CH}_2)_r\text{N(R}^6)\text{SO}_2\text{R}^6$, $-(\text{CH}_2)_r\text{OC(O)}\text{N(R}^2)(\text{R}^6)$, -
 $(\text{CH}_2)_r\text{OC(O)}\text{N(R}^2)(\text{R}^2)$, $-(\text{CH}_2)_r\text{SO}_2\text{N(R}^2)(\text{R}^6)$, -
 10 $(\text{CH}_2)_r\text{OC(O)}\text{N(R}^2)(\text{R}^2)$, $-(\text{CH}_2)_r\text{SO}_2\text{N(R}^2)(\text{R}^6)$, -
 $(\text{CH}_2)_r\text{SO}_2\text{N(R}^2)(\text{R}^2)$, $-(\text{CH}_2)_r\text{N(R}^2)\text{SO}_2\text{N(R}^2)(\text{R}^6)$, -
 $(\text{CH}_2)_r\text{N(R}^6)\text{SO}_2\text{N(R}^2)(\text{R}^6)$, $-(\text{CH}_2)_r\text{S(O)}_m\text{R}^6$, and $-(\text{CH}_2)_r\text{S(O)}_m\text{R}^2$;

- R^{3a} and R^{3b} are independently selected from: hydrogen, phenyl,
 15 phenoxy, halophenyl, $\text{-C}_1\text{-C}_6$ alkyl, halogen, -OR^2 , methylenedioxy, -
 $\text{S(O)}_m\text{R}^2$, -CF_3 , -OCF_3 , nitro, $\text{-N(R}^2)(\text{R}^2)$, $\text{-N(R}^2)\text{C(O)}(\text{R}^2)$, -C(O)OR^2 ,
 $\text{-C(O)N(R}^2)(\text{R}^2)$, $\text{-SO}_2\text{N(R}^2)(\text{R}^2)$, $\text{-N(R}^2)\text{SO}_2\text{-aryl}$, and $\text{-N(R}^2)\text{SO}_2\text{R}^2$;

E is selected from: -O- , -S- , -CH=CH- ,



20

which is optionally substituted with a substituent selected
 from: halo, hydroxy, $\text{-N(R}^2)(\text{R}^2)$, $\text{C}_1\text{-C}_6$ alkyl and $\text{C}_1\text{-C}_6$ alkoxy;

- 6 -

R^4 and R^5 are independently selected from hydrogen, C₁-C₆ alkyl, and substituted C₁-C₆ alkyl where the substituents are selected from halo, hydroxy, phenyl, and C₁-C₆ alkoxy carbonyl;

or R^5 and R^4 may be taken together to form $-(CH_2)_d-L_a(CH_2)_e-$ where

- 5 L_a is $-C(R^2)_2-$, $-O-$, $-S(O)_m-$ or $-N(R^2)-$, d and e are independently 1 to 3 and R^2 is as defined above;

R^{4a} and R^{4b} are independently selected from: hydrogen, C₁-C₆ alkyl, trifluoromethyl, phenyl, or substituted C₁-C₆ alkyl where the substituents

- 10 are selected from: imidazolyl, naphthyl, phenyl, indolyl, p-hydroxyphenyl, $-OR^2$, $-S(O)_mR^2$, $-C(O)OR^2$, C₃-C₇ cycloalkyl, $-N(R^2)(R^2)$, $-C(O)N(R^2)(R^2)$; or R^{4a} and R^{4b} may independently be joined to one or both of R^4 or E (where E is other than $-O-$, $-S-$, or $-CH=CH-$) to form an alkylene bridge between the terminal nitrogen and
- 15 the alkyl portion of the R^{4a} or R^{4b} and the R^4 E group, wherein the bridge contain 1 to 8 carbons atoms; or R^{4a} and R^{4b} may be joined to one another to form C₃-C₇ cycloalkyl;

R^6 is selected from: hydrogen, C₁-C₆ alkyl, and $(CH_2)_v$ aryl, wherein

- 20 the $(CH_2)_v$ and alkyl groups may be optionally substituted by $-O(R^2)$, $-S(O)_mR^2$, $-C(O)OR^2$, $-C(O)N(R^2)(R^2)$, $-SO_2N(R^2)(R^2)$, or $-N(R^2)C(O)N(R^2)(R^2)$, wherein the aryl group is selected from: phenyl, pyridyl, 1H-tetrazolyl, triazolyl, oxadiazolyl, pyrazolyl, thiadiazoyl, and benzimidazol-2-yl, which is optionally substituted with C₁-C₆ alkyl, C₃-
- 25 C₆ cycloalkyl, amino, or hydroxyl;

X is selected from the group consisting of: hydrogen, $-C\equiv N$, -

- $(CH_2)_qN(R^2)C(O)R^2$, $-(CH_2)_qN(R^2)C(O)(CH_2)_t$ aryl, -
 $(CH_2)_qN(R^2)SO_2(CH_2)_t$ aryl, $-(CH_2)_qN(R^2)SO_2R^2$, -
 30 $(CH_2)_qN(R^2)C(O)N(R^2)(CH_2)_t$ aryl, $-(CH_2)_qN(R^2)C(O)N(R^2)(R^2)$, -
 $(CH_2)_qC(O)N(R^2)(R^2)$, $-(CH_2)_qC(O)N(R^2)(CH_2)_t$ aryl, -
 $(CH_2)_qC(O)OR^2$, $-(CH_2)_qC(O)O(CH_2)_t$ aryl, $-(CH_2)_qOR^2$, -
 $(CH_2)_qOC(O)R^2$, $-(CH_2)_qOC(O)(CH_2)_t$ aryl, $-(CH_2)_qOC(O)N(R^2)(R^2)$,

- 7 -

- $-(CH_2)_qC(O)R^2$, $-(CH_2)_qC(O)(CH_2)_t\text{aryl}$, $-(CH_2)_qN(R^2)C(O)OR^2$, $-(CH_2)_qN(R^2)SO_2N(R^2)(R^2)$, $-(CH_2)_qS(O)_mR^2$, and $-(CH_2)_qS(O)_m(CH_2)_t\text{aryl}$, where R^2 , $(CH_2)_q$ and $(CH_2)_t$ group may be optionally substituted with C₁-C₄ alkyl, hydroxyl, C₁-C₄ lower alkoxy, carboxyl, $N(R^2)(R^2)$, $CONH_2$, $S(O)_mCH_3$, carboxylate C₁-C₄ alkyl esters, or 1H-tetrazol-5-yl, and aryl is phenyl, naphthyl, pyridyl, thiazolyl, or 1H-tetrazol-5-yl groups which may be optionally substituted with halogen, $-OR^2$, $-CON(R^2)(R^2)$, $-C(O)OR^2$, C₁-C₄ alkyl, $-S(O)_mR^2$, or 1H-tetrazol-5-yl;
- Y is selected from the group consisting of:
 hydrogen, C₁-C₁₀ alkyl, $-(CH_2)_t\text{aryl}$,
 $-(CH_2)_q(C_3\text{-}C_7\text{ cycloalkyl})$, $-(CH_2)_q\text{-K-(C}_1\text{-C}_6\text{ alkyl)}$, $-(CH_2)_q\text{-K-(CH}_2)_t\text{aryl}$, $-(CH_2)_q\text{-K-(CH}_2)_t(C_3\text{-}C_7\text{ cycloalkyl containing O, NR}^2\text{ S)}$ and $-(CH_2)_q\text{-K-(CH}_2)_t(C_3\text{-}C_7\text{ cycloalkyl)}$, where K is $-O-$, $-S(O)_m-$, $-C(O)NR^2-$, $-\text{CH=CH}-$, $-\text{C}\equiv\text{C}-$, $-N(R^2)C(O)-$, $-C(O)NR^2-$, $-C(O)O-$, or $-OC(O)-$, and where the alkyl, R^2 , $(CH_2)_q$ and $(CH_2)_t$ groups are optionally substituted by C₁-C₄ alkyl, hydroxyl, C₁-C₄ lower alkoxy, carboxyl, $-\text{CONH}_2$ or a carboxylate C₁-C₄ alkyl ester, and aryl is phenyl, naphthyl, pyridyl, 1-H-tetrazol-5-yl, thiazolyl, imidazolyl, indolyl, oxadiazolyl, pyrimidinyl, thiadiazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiophenyl, quinolinyl, pyrazinyl, or isothiazolyl which is optionally substituted with halogen, $-OR^2$, $-C(O)OR^2$, $N(R^2)(R^2)$, $-C(O)N(R^2)(R^2)$, nitro, cyano, benzyl, C₁-C₄ alkyl, $-S(O)_mR^2$, or 1H-tetrazol-5-yl;

- D is selected from: $-N(R^7)-$, $-S(O)_m-$, $-C(O)-$ and $-C(H)(R^7)-$, wherein R^7 is selected from: $-R^2$, $-OR^2$, $-(CH_2)_q\text{aryl}$, $-C(O)R^2$, $-C(O)(CH_2)_q\text{aryl}$, $-\text{SO}_2R^2$, $-\text{SO}_2(CH_2)_q\text{aryl}$, $-C(O)N(R^2)(R^2)$, $-C(O)N(R^2)(CH_2)_q\text{aryl}$, $-C(O)OR^2$, 1-H-tetrazol-5-yl, $-\text{SO}_2N(R^2)\text{aryl}$, $-\text{SO}_2N(R^2)(R^2)$ and the $(CH_2)_q$ may be optionally substituted by C₁-C₄ alkyl, and the R^2 and aryl may be optionally further substituted with a substituent selected from: $-OR^{2a}$, $-O(CH_2)_q\text{aryl}$, $-C(O)OR^{2a}$, -

- 8 -

C(O)(CH₂)_q aryl, -C(O)N(R^{2a})(R^{2a}), -C(O)N(R^{2a})(CH₂)₁ aryl,
 halogen, -N(R^{2a})(R^{2a}), -C₁-C₄ alkyl, 1,2,4-triazolyl, 1-H-tetrazol-5-yl, -
 C(O)NHSO₂R^{2a}, -S(O)_mR^{2a}, -C(O)NHSO₂(CH₂)_qaryl, -
 N(R²)C(O)N(R^{2a})(R^{2a}), -N(R^{2a})C(O)N(R^{2a})(CH₂)_qaryl, -
 5 N(R^{2a})(R^{2a}), -N(R^{2a})C(O)R^{2a}, -N(R^{2a})C(O)(CH₂)_q aryl, -
 OC(O)N(R^{2a})(R^{2a}), -OC(O)N(R^{2a})(CH₂)_q aryl;

1 is 0, 1 or 2;
 m is 0, 1, or 2;
 10 n is 0, 1, or 2;
 q is 0, 1, 2, 3, or 4;
 r is 0, 1, 2, or 3;
 t is 0, 1, 2, or 3;
 v is 0, 1, or 2;
 15 x is 0, 1, 2, or 3;
 y is 0, 1, 2, or 3, with the proviso that if E is -O- or -S-, y is other than 0
 or 1, and with the further proviso that if E is -CH=CH-, y is other than 0;

and pharmaceutically acceptable salts and individual diastereomers
 20 thereof.

In the above structural formula and throughout the instant
 specification, the following terms have the indicated meanings:

25 When n is 1 a pyrrolidine ring is formed, when n is 2 a
 piperidine ring is formed, and when n is 3 the ring is designated a
 hexahydro-1-H-azepine.

The alkyl groups specified above are intended to include
 those alkyl groups of the designated length in either a straight or
 30 branched configuration and if two carbon atoms or more they may
 include a double or a triple bond. Exemplary of such alkyl groups are
 methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, tertiary butyl, pentyl,
 isopentyl, hexyl, isohexyl, allyl, propargyl, and the like .

- 9 -

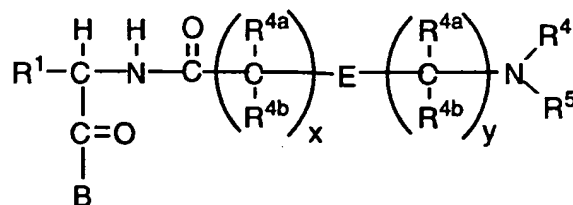
The alkoxy groups specified above are intended to include those alkoxy groups of the designated length in either a straight or branched configuration and if two or more carbon atoms in length, they may include a double or a triple bond. Exemplary of such alkoxy groups are methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, tertiary butoxy, pentoxy, isopentoxy, hexoxy, isohexoxy allyloxy, propargyloxy, and the like.

The term "halogen" is intended to include the halogen atom fluorine, chlorine, bromine and iodine.

The term "aryl" within the present invention, unless otherwise specified, is intended to include aromatic rings, such as carbocyclic and heterocyclic aromatic rings selected the group consisting of: phenyl, naphthyl, pyridyl, 1-H-tetrazol-5-yl, thiazolyl, imidazolyl, indolyl, pyrimidinyl, thiadiazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiophenyl, quinolinyl, pyrraziny, or isothiazolyl, which may be optionally substituted by 1 to 3 of C₁-C₆ alkyl, 1 to 3 of halogen, 1 to 2 of OR₂, methylenedioxy, -S(O)_mR₂, 1 to 2 of -CF₃, -OCF₃, nitro, -N(R₂)C(O)(R₂), -C(O)OR₂, -C(O)N(R₂)(R₂), -1H-tetrazol-5-yl, -SO₂N(R₂)(R₂), -N(R₂)SO₂ phenyl, or -N(R₂)SO₂R₂, wherein R₂ is as defined herein.

Certain of the above defined terms may occur more than once in the above formula and upon such occurrence each term shall be defined independently of the other.

Preferred compounds of the instant invention include those of Formula Ia:



Formula Ia

wherein:

R¹ is selected from the group consisting of:
 C₁-C₁₀ alkyl, -aryl-, aryl (C₁-C₆ alkyl)-,
 heteroaryl-, heteroaryl(C₁-C₆ alkyl)-,

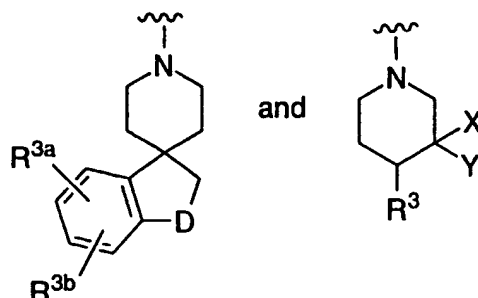
- 10 -

- (C3-C7 cycloalkyl)-(C1-C6 alkyl)-,
 (C1-C5 alkyl)-K-(C1-C5 alkyl)-,
 aryl-(C0-C5 alkyl)-K-(C1-C5 alkyl)-,
 heteroaryl-(C0-C5 alkyl)-K-(C1-C5 alkyl)-, and
 5 (C3-C7 cycloalkyl)-(C0-C5 alkyl)-K-(C1-C5 alkyl)-,
 wherein K is -O-, -S(O)_m-, -N(R²)C(O)-, -C(O)N(R²)-, -OC(O)-,
 -C(O)O-, -CR²=CR²- or -C≡C-,
 wherein R² and the alkyl groups may be further substituted with 1 to 9
 halo, -S(O)_mR^{2a}, 1 to 3 of -OR^{2a}, or -C(O)OR^{2a}, and wherein aryl is
 10 phenyl or naphthyl, and heteroaryl is selected from indolyl, thiophenyl,
 benzofuranyl, benzothiopheneyl, aza-indolyl, pyridinyl, quinolinyl, and
 benzimidazolyl, wherein aryl and heteroaryl are unsubstituted or
 substituted with phenyl, phenoxy, halophenyl, 1 to 3 of -C1-C6 alkyl, 1 to
 3 of halo, 1 to 2 of -OR², methylenedioxy, -S(O)_mR², 1 to 2 of -CF₃, -
 15 OCF₃, nitro, -N(R²)(R²), -N(R²)C(O)(R²), -C(O)OR², -C(O)N(R²)(R²),
 -SO₂N(R²)(R²), -N(R²)SO₂-aryl, or -N(R²)SO₂R²;

- R² is selected from the group consisting of:
 hydrogen, -C1-C6 alkyl, -C3-C7 cycloalkyl, and -CH₂-phenyl,
 20 wherein the alkyl or the cycloalkyl is unsubstituted or substituted with
 hydroxyl, C1-C3 alkoxy, thioalkyl, -C(O)OR^{2a}, and wherein, if two
 -C1-C6 alkyl groups are present on one atom, the groups may be
 optionally joined to form a C3-C8 cyclic ring being selected from the
 group consisting of pyrrolidine, piperidine, piperazine, morpholine,
 25 thiomorpholine;

B is selected from:

- 11 -

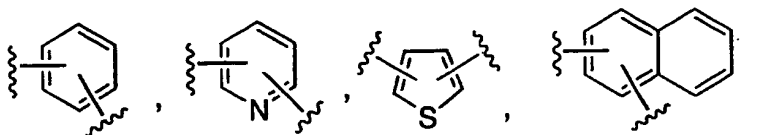


R^3 is selected from: hydrogen, phenyl, pyridyl, naphthyl, indolyl, benzimidazolyl, thienyl, quinoliny, where the phenyl, pyridyl, naphthyl, benzimidazolyl, thienyl, quinoliny, and indolyl may be substituted by 1 to 3 substituents selected from the group consisting of: C₁-C₆ alkyl, halogen, -OR², -(CH₂)_rOR⁶, -(CH₂)_rN(R²)(R⁶), -(CH₂)_r(R⁶), -(CH₂)_rC(O)OR², -(CH₂)_rC(O)OR⁶, -(CH₂)_rC(O)R², -(CH₂)_rC(O)R⁶, -(CH₂)_rC(O)N(R²)(R²), -(CH₂)_rC(O)N(R²)(R⁶), -(CH₂)_rN(R²)C(O)(R²), -(CH₂)_rN(R²)C(O)R⁶, -(CH₂)_rN(R⁶)C(O)R², -(CH₂)_rN(R⁶)C(O)R⁶, -(CH₂)_rN(R²)C(O)OR², -(CH₂)_rN(R²)C(O)OR⁶, -(CH₂)_rN(R⁶)C(O)OR², -(CH₂)_rN(R⁶)C(O)OR⁶, -(CH₂)_rN(R²)C(O)N(R²)(R⁶), -(CH₂)_rN(R²)C(O)N(R²)(R²), -(CH₂)_rN(R⁶)C(O)N(R²)(R⁶), -(CH₂)_rN(R²)SO₂R², -(CH₂)_rN(R⁶)SO₂R², -(CH₂)_rN(R⁶)SO₂R⁶, -(CH₂)_rOC(O)N(R²)(R⁶), -(CH₂)_rSO₂N(R²)(R⁶), -(CH₂)_rSO₂N(R²)(R²), -(CH₂)_rS(O)_mR⁶, and -(CH₂)_rS(O)_mR²;

R^{3a} and R^{3b} are independently selected from: hydrogen, phenyl, phenoxy, halophenyl, -C₁-C₆ alkyl, halogen, -OR², methylenedioxy, -S(O)_mR², -CF₃, -OCF₃, nitro, -N(R²)(R²), -N(R²)C(O)(R²), -C(O)OR², -C(O)N(R²)(R²), -SO₂N(R²)(R²), -N(R²)SO₂-aryl, and -N(R²)SO₂R²;

E is selected from: -O-, -S-, -CH=CH-,

- 12 -



which is optionally substituted with a substituent selected from: halo, hydroxy, $-N(R^2)(R^2)$, C_1 - C_6 alkyl and C_1 - C_6 alkoxy;

- 5 R^4 and R^5 are independently selected from hydrogen, C_1 - C_6 alkyl, and substituted C_1 - C_6 alkyl where the substituents are selected from halo, hydroxy, phenyl, and C_1 - C_6 alkoxycarbonyl;
 or R^5 and R^4 may be taken together to form $-(CH_2)_d-L_a(CH_2)_e-$ where L_a is $-C(R^2)_2-$, $-O-$, $-S(O)_m-$ or $-N(R^2)-$, d and e are independently 1 to 3
 10 and R^2 is as defined above;

- R^{4a} and R^{4b} are independently selected from: hydrogen, C_1 - C_6 alkyl, trifluoromethyl, phenyl, or substituted C_1 - C_6 alkyl where the substituents are selected from: imidazolyl, naphthyl, phenyl, indolyl,
 15 p-hydroxyphenyl, $-OR^2$, $-S(O)_mR^2$, $-C(O)OR^2$, C_3 - C_7 cycloalkyl, $-N(R^2)(R^2)$, $-C(O)N(R^2)(R^2)$; or R^{4a} and R^{4b} may independently be joined to one or both of R^4 or E (where E is other than $-O-$, $-S-$, or $-CH=CH-$) to form an alkylene bridge between the terminal nitrogen and the alkyl portion of the R^{4a} or R^{4b} and the R^4 E group, wherein the
 20 bridge contain 1 to 5 carbons atoms; or R^{4a} and R^{4b} may be joined to one another to form C_3 - C_7 cycloalkyl;

- R^6 is selected from: hydrogen, C_1 - C_6 alkyl, and $(CH_2)_v$ aryl, wherein the $(CH_2)_v$ and alkyl groups may be optionally substituted by $-O(R^2)$, $-S(O)_mR^2$, $-C(O)OR^2$, $-C(O)N(R^2)(R^2)$, $-SO_2N(R^2)(R^2)$, or $-N(R^2)C(O)N(R^2)(R^2)$, wherein the aryl group is selected from: phenyl,
 25 pyridyl, 1H-tetrazolyl, triazolyl, oxadiazolyl, pyrazolyl, thiadiazoyl, and benzimidazol-2-yl, which is optionally substituted with C_1 - C_6 alkyl, C_3 - C_6 cycloalkyl, amino, or hydroxyl;

30

- 13 -

X is selected from the group consisting of: hydrogen, $-C\equiv N$, -
 $(CH_2)_qN(R^2)C(O)R^2$, $-(CH_2)_qN(R^2)C(O)(CH_2)_taryl$, -
 $(CH_2)_qN(R^2)SO_2(CH_2)_taryl$, $-(CH_2)_qN(R^2)SO_2R^2$, -
 $(CH_2)_qN(R^2)C(O)N(R^2)(CH_2)_taryl$, $-(CH_2)_qN(R^2)C(O)N(R^2)(R^2)$, -
5 $(CH_2)_qC(O)N(R^2)(R^2)$, $-(CH_2)_qC(O)N(R^2)(CH_2)_taryl$, -
 $(CH_2)_qC(O)OR^2$, $-(CH_2)_qC(O)O(CH_2)_taryl$, $-(CH_2)_qOR^2$, -
 $(CH_2)_qOC(O)R^2$, $-(CH_2)_qOC(O)(CH_2)_taryl$, $-(CH_2)_qOC(O)N(R^2)(R^2)$,
 $-(CH_2)_qC(O)R^2$, $-(CH_2)_qC(O)(CH_2)_taryl$, $-(CH_2)_qN(R^2)C(O)OR^2$, -
 $(CH_2)_qN(R^2)SO_2N(R^2)(R^2)$, $-(CH_2)_qS(O)_mR^2$, and -
10 $(CH_2)_qS(O)_m(CH_2)_taryl$, where R^2 , $(CH_2)_q$ and $(CH_2)_t$ group may be
optionally substituted with C1-C4 alkyl, hydroxyl, C1-C4 lower alkoxy,
carboxyl, $N(R^2)(R^2)$, $CONH_2$, $S(O)_mCH_3$, carboxylate C1-C4 alkyl
esters, or 1H-tetrazol-5-yl, and aryl is phenyl, naphthyl, pyridyl, thiazolyl,
or 1H-tetrazol-5-yl groups which may be optionally substituted with
15 halogen, $-OR^2$, $-CON(R^2)(R^2)$, $-C(O)OR^2$, C1-C4 alkyl, $-S(O)_mR^2$, or
1H-tetrazol-5-yl;

Y is selected from the group consisting of:
hydrogen, C1-C10 alkyl, $-(CH_2)_taryl$,
20 $-(CH_2)_q(C_3-C_7 \text{ cycloalkyl})$, $-(CH_2)_qK-(C_1-C_6 \text{ alkyl})$, $-(CH_2)_qK-$
 $(CH_2)_taryl$, $-(CH_2)_qK-(CH_2)_t(C_3-C_7 \text{ cycloalkyl containing O, } NR^2 \text{ S})$
and $-(CH_2)_qK-(CH_2)_t(C_3-C_7 \text{ cycloalkyl})$, where K is O, $S(O)_m$,
 $C(O)NR^2$, $CH=CH$, $C\equiv C$, $N(R^2)C(O)$, $C(O)NR^2$, $C(O)O$, or $OC(O)$, and
where the alkyl, R^2 , $(CH_2)_q$ and $(CH_2)_t$ groups are optionally substituted
25 by C1-C4 alkyl, hydroxyl, C1-C4 lower alkoxy, carboxyl, $-CONH_2$ or a
carboxylate C1-C4 alkyl ester, and aryl is phenyl, naphthyl, pyridyl, 1-H-
tetrazol-5-yl, thiazolyl, imidazolyl, indolyl, oxadiazoyl, pyrimidinyl,
thiadiazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiophenyl, quinolinyl,
pyrazinyl, or isothiazolyl which is optionally substituted with halogen, -
30 OR^2 , $-C(O)OR^2$, $N(R^2)(R^2)$, $-C(O)N(R^2)(R^2)$, nitro, cyano, benzyl, C1-
C4 alkyl, $-S(O)_mR^2$, or 1H-tetrazol-5-yl;

D is selected from: $-N(R^7)-$, $-S(O)_m-$, $-C(O)-$ and $-C(H)(R^7)-$,

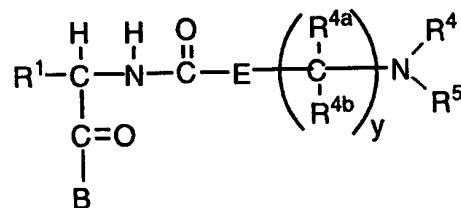
- 14 -

wherein R^7 is selected from: $-R^2$, $-(CH_2)_q\text{aryl}$, $-C(O)R^2$, $-SO_2R^2$, $-C(O)N(R^2)(R^2)$, $-C(O)OR^2$, 1-H-tetrazol-5-yl, $-SO_2N(R^2)\text{aryl}$, $-SO_2N(R^2)(R^2)$ and the $(CH_2)_q$ may be optionally substituted by C_1 - C_4 alkyl, and the R^2 and aryl may be optionally further substituted with a
 5 substituent selected from: $-OR^{2a}$, $-C(O)OR^{2a}$, $-C(O)N(R^{2a})(R^{2a})$, halogen, $-C_1$ - C_4 alkyl, and the aryl is selected from triazolyl, oxadiazolyl, thiadiazolyl, thiazolyl, imidazolyl, and 1H-tetrazolyl;

1 is 0, 1 or 2;
 10 m is 0, 1, or 2;
 q is 0, 1, 2, 3, or 4;
 r is 0, 1, 2, or 3;
 t is 0, 1, 2, or 3;
 v is 0, 1, or 2;
 15 x is 0, 1, 2, or 3;
 y is 0, 1, 2, or 3, with the proviso that if E is -O- or -S-, y is other than 0 or 1, and with the further proviso that if E is $-CH=CH-$, y is other than 0;

and pharmaceutically acceptable salts and individual diastereomers
 20 thereof.

More preferred compounds of the instant invention include those of Formula Ib:



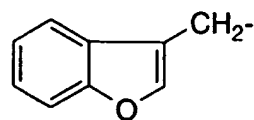
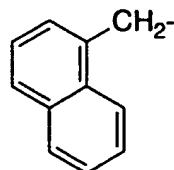
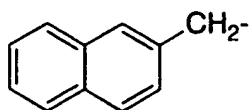
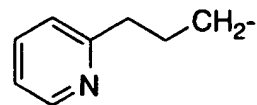
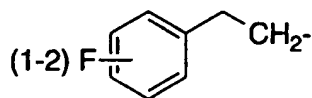
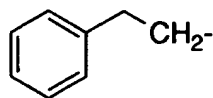
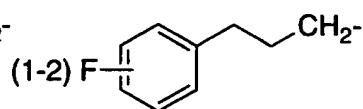
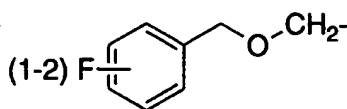
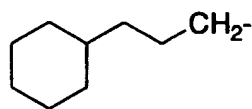
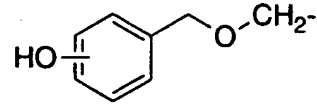
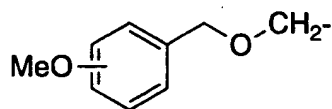
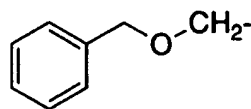
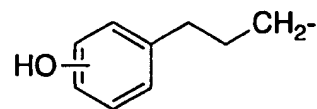
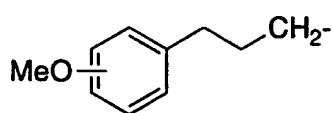
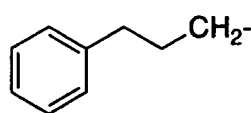
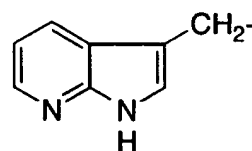
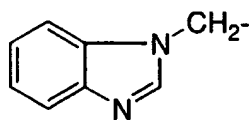
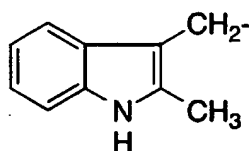
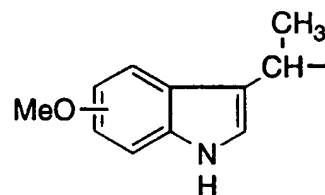
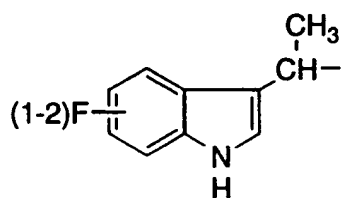
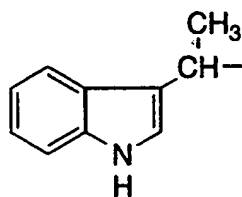
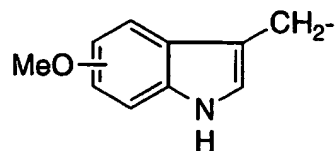
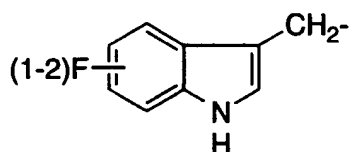
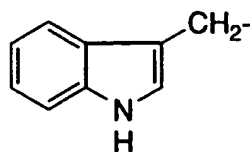
25

Formula Ib

wherein:

R^1 is selected from the group consisting of:

- 15 -



- 16 -

or their regioisomers where not specified;

R² is selected from the group consisting of:

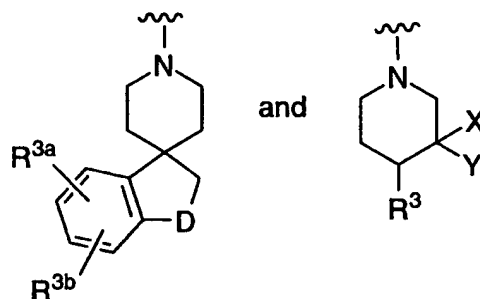
hydrogen, -C₁-C₆ alkyl, -C₃-C₇ cycloalkyl, and -CH₂-phenyl,

- 5 wherein the alkyl or the cyloalkyl is unsubstituted or substituted with hydroxyl; C₁-C₃ alkoxy, thioalkyl, -C(O)OR^{2a}, and wherein, if two -C₁-C₆ alkyl groups are present on one atom, the groups may be optionally joined to form a C₃-C₈ cyclic ring being selected from the group consisting of pyrrolidine, piperidine, piperazine, morpholine,
- 10 thiomorpholine;

R^{2a} is hydrogen, or C₁-C₄ alkyl;

- 17 -

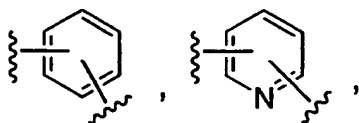
B is selected from:



R^3 is selected from: hydrogen or phenyl, wherein the phenyl is substituted in the ortho position by a substituent selected from the group consisting of: C1-C6 alkyl, halogen, $-OR^2$, $-(CH_2)_rOR^6$, $-(CH_2)_rN(R^2)(R^6)$, $-(CH_2)_r(R^6)$, $-(CH_2)_rC(O)OR^2$, $-(CH_2)_rC(O)OR^6$, $-(CH_2)_rC(O)R^2$, $-(CH_2)_rC(O)R^6$, $-(CH_2)_rC(O)N(R^2)(R^2)$, $-(CH_2)_rC(O)N(R^2)(R^6)$, $-(CH_2)_rSO_2N(R^2)(R^6)$, $-(CH_2)_rSO_2N(R^2)(R^2)$, $-(CH_2)_rS(O)_mR^6$, and $-(CH_2)_rS(O)_mR^2$;

R^{3a} and R^{3b} are independently selected from: hydrogen, -C1-C6 alkyl and halogen;

E is selected from: -O-, -CH=CH-,



which is optionally substituted with a substituent selected from: halo, hydroxy, $-N(R^2)(R^2)$, C1-C6 alkyl and C1-C6 alkoxy;

R^4 and R^5 are independently selected from hydrogen, C1-C6 alkyl, and substituted C1-C6 alkyl where the substituents are selected from halo, hydroxy, phenyl, and C1-C6 alkoxy carbonyl;

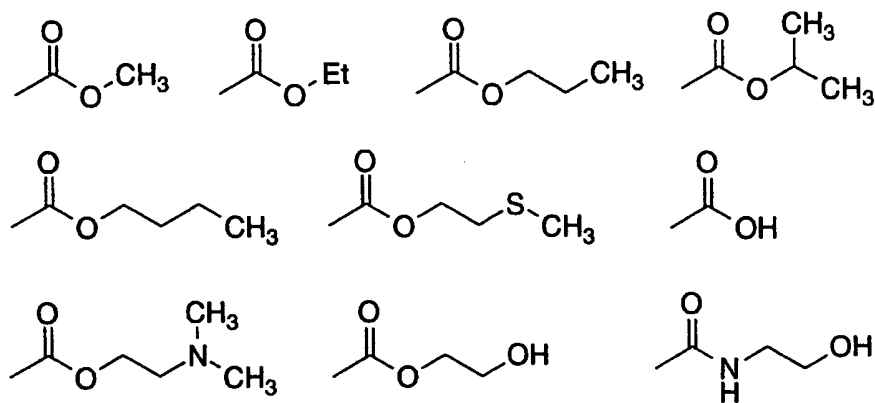
- 18 -

or R^5 and R^4 may be taken together to form $-(CH_2)_d-L_a(CH_2)_e-$ where L_a is $-C(R^2)_2-$, $-O-$, $-S(O)_m-$ or $-N(R^2)-$, d and e are independently 1 to 3 and R^2 is as defined above;

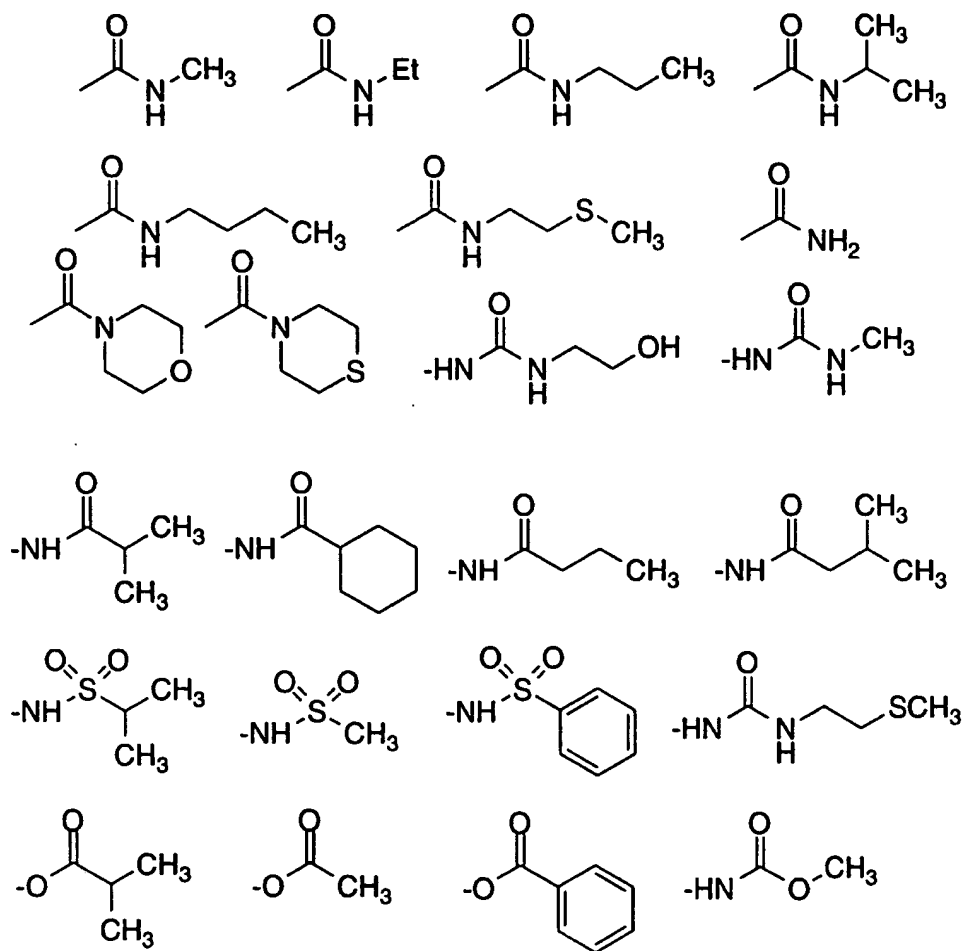
- 5 R^{4a} and R^{4b} are independently selected from: hydrogen, C_1 - C_6 alkyl, or substituted C_1 - C_6 alkyl where the substituents are selected from: imidazolyl, naphthyl, phenyl, indolyl, and p-hydroxyphenyl;

- R^6 is selected from: hydrogen, C_1 - C_6 alkyl, and $(CH_2)_v$ aryl, wherein
 10 the $(CH_2)_v$ and alkyl groups may be optionally substituted by $-O(R^2)$, $-S(O)_mR^2$, $-C(O)OR^2$, $-C(O)N(R^2)(R^2)$, $-SO_2N(R^2)(R^2)$, or $-N(R^2)C(O)N(R^2)(R^2)$, wherein the aryl group is selected from: phenyl, pyridyl, 1H-tetrazolyl, triazolyl, oxadiazolyl, pyrazolyl, thiadiazolyl, and benzimidazol-2-yl, which is optionally substituted with C_1 - C_6 alkyl, C_3 -
 15 C_6 cycloalkyl, amino, or hydroxyl;

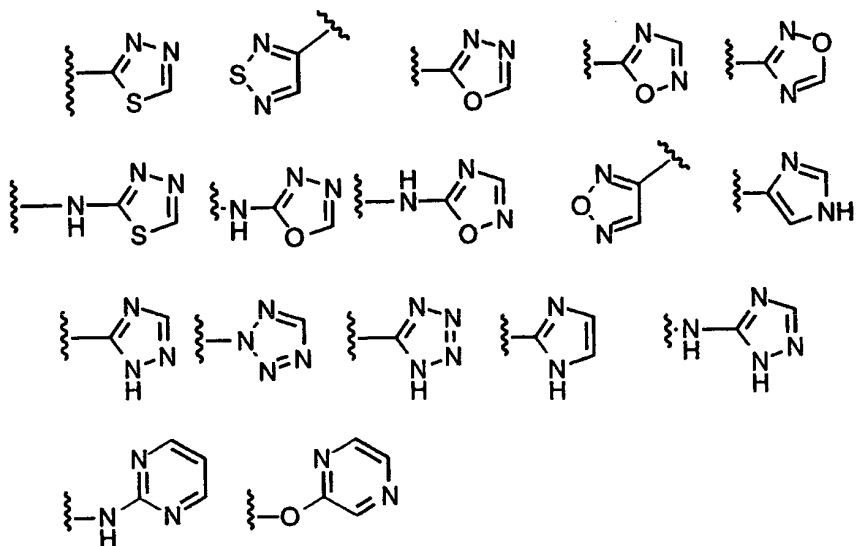
X is selected from the group consisting of: hydrogen,



- 19 -



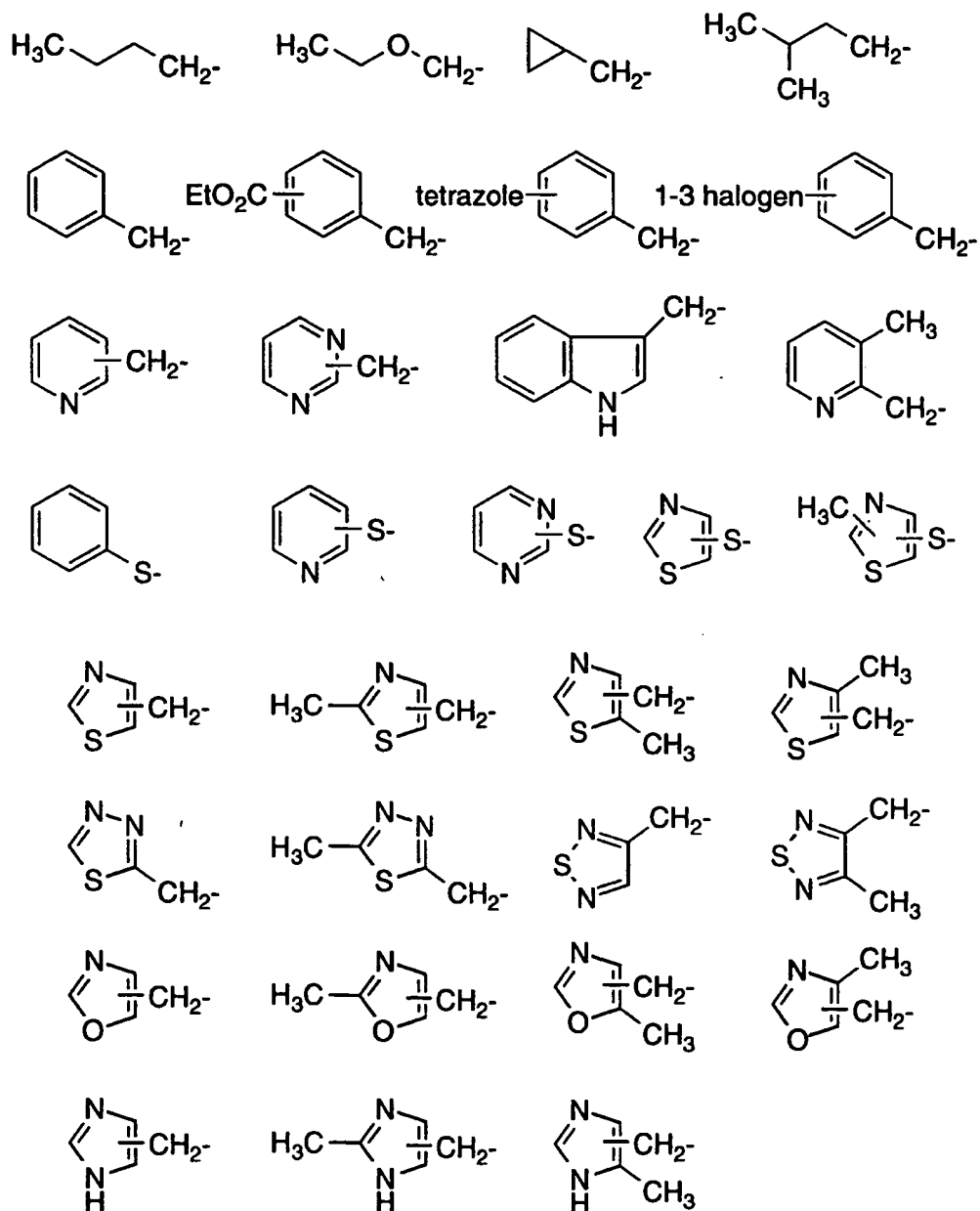
and further selected from the following group of heterocycles



wherein the heterocycle is optionally substituted with a substituent selected from: -N(R²)(R²), -O(R²), C₁-C₃ alkyl, halogen, and trifluoromethyl;

- 21 -

Y is selected from the group consisting of: hydrogen,



5

or their regioisomers whereof where not specified;

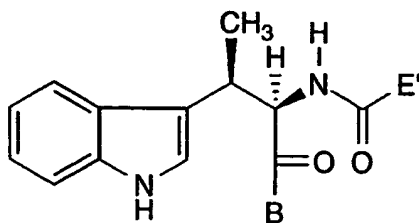
- 22 -

- D is selected from: $-N(R^7)-$, $-S(O)_m-$, $-C(O)-$ and $-C(H)(R^7)-$,
 wherein R^7 is selected from: $-R^2$, $-(CH_2)_q\text{aryl}$, $-C(O)R^2$, $-SO_2R^2$, $-C(O)N(R^2)(R^2)$, $-C(O)OR^2$, 1-H-tetrazol-5-yl, $-SO_2N(R^2)\text{aryl}$, $-SO_2N(R^2)(R^2)$ and the $(CH_2)_q$ may be optionally substituted by C₁-C₄
 5 alkyl, and the R^2 and aryl may be optionally further substituted with a
 substituent selected from: $-OR^{2a}$, $-C(O)OR^{2a}$, $-C(O)N(R^{2a})(R^{2a})$,
 halogen, -C₁-C₄ alkyl, and the aryl is selected from of triazolyl,
 oxadiazolyl, 1H-tetrazolyl, and thiadiazolyl;
- 10 l is 0, 1 or 2;
 m is 0, 1, or 2;
 q is 0, 1, 2, 3, or 4;
 r is 0, 1, 2, or 3;
 t is 0, 1, 2, or 3;
 15 v is 0, 1, or 2;
 y is 1 or 2, with the proviso that if E is -O-, y is 2;

and pharmaceutically acceptable salts and individual diastereomers thereof.

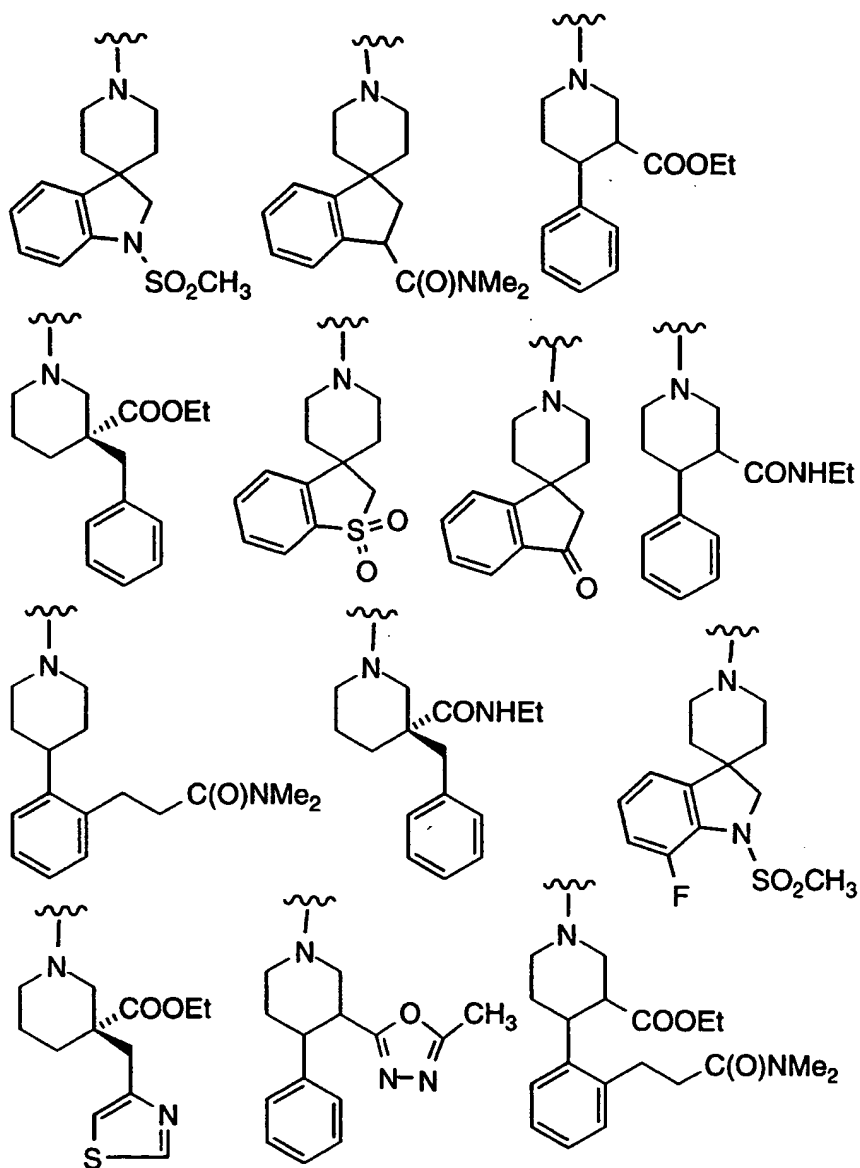
20

The most preferred compounds of the instant invention include compounds of the formula:



wherein B is selected from the group consisting of:

- 23 -



E' is selected from:

-CH=CH-CH₂-NH₂, -CH=CH-CH(CH₃)-NH₂,

-CH=CH-C(CH₃)₂-NH₂,

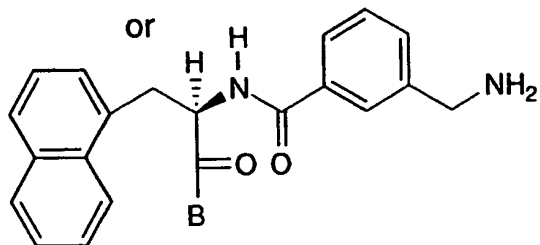
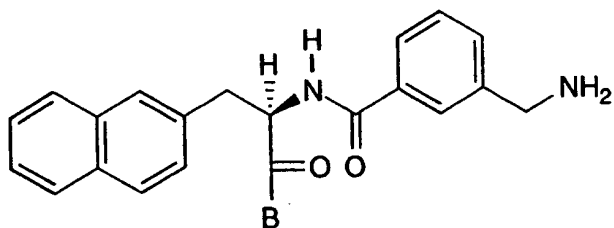
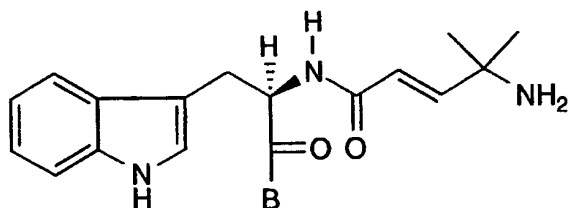
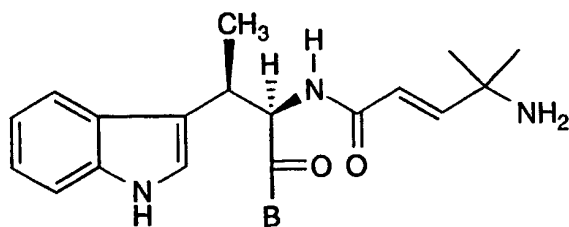
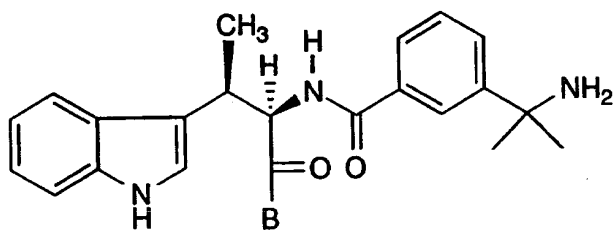
5

or phenyl substituted with -CH₂-NH₂, -CH(CH₃)-NH₂,

or -C(CH₃)₂-NH₂;

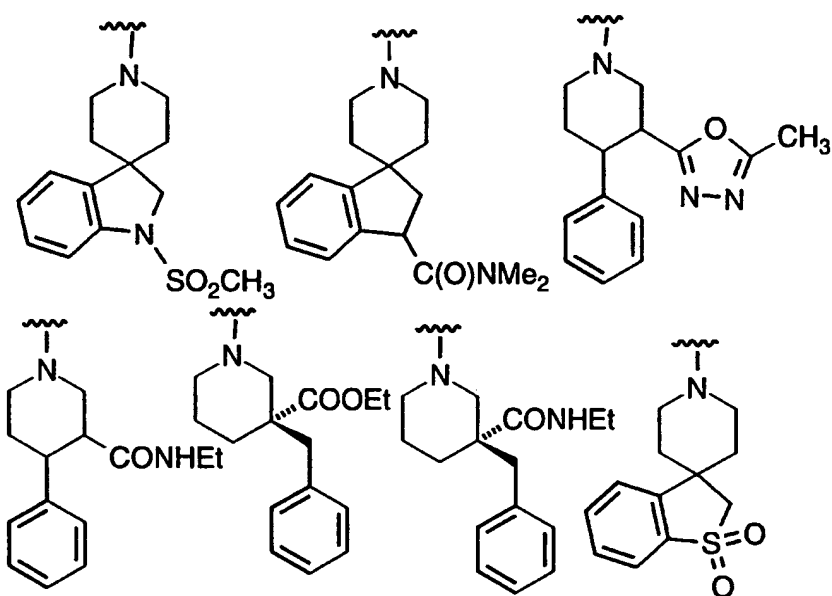
and pharmaceutically acceptable salts and individual diastereomers thereof.

The even more preferred compounds of the instant invention include compounds of the formula:



- 25 -

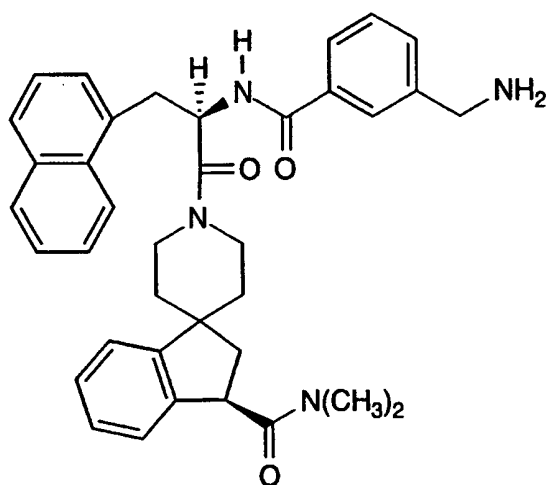
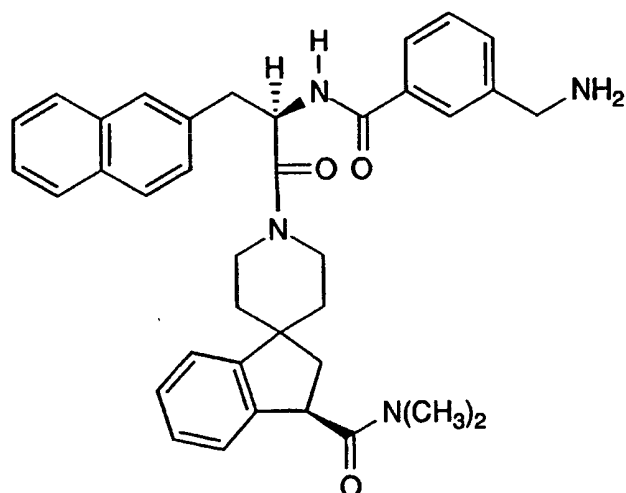
wherein B is selected from the group consisting of:



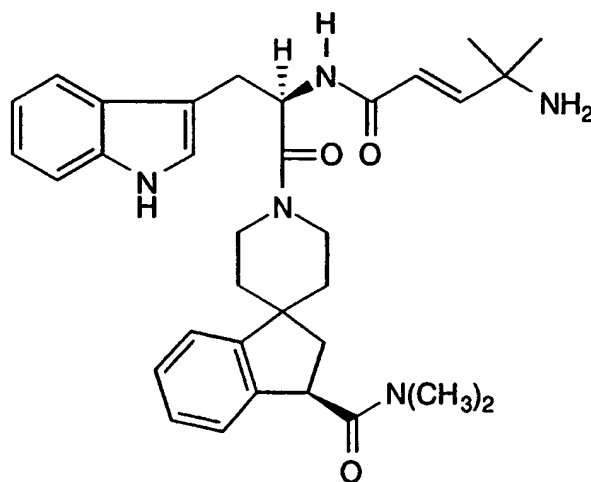
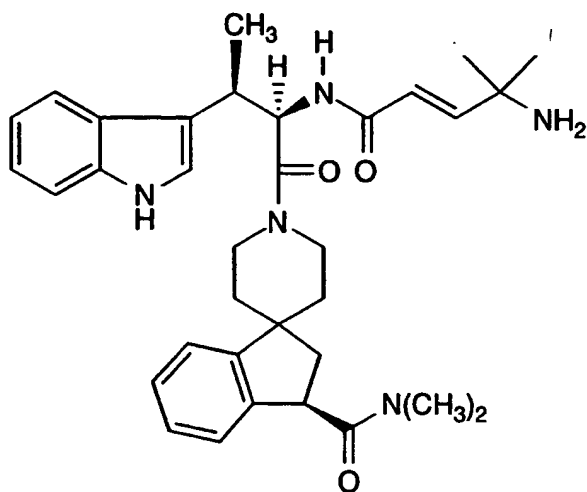
and pharmaceutically acceptable salts and individual diastereomers thereof.

- 26 -

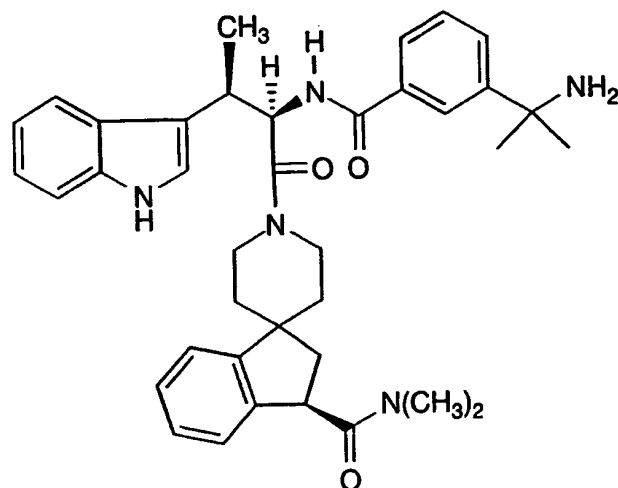
Specific compounds within the instant invention include the following:



- 27 -



- 28 -



and pharmaceutically acceptable salts and individual diastereomers thereof where not otherwise specified.

- 29 -

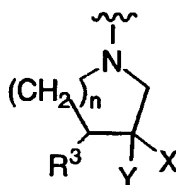
Throughout the instant application, the following abbreviations are used with the following meanings:

	Bu	butyl
	Bn	benzyl
5	BOC, Boc	t-butyloxycarbonyl
	BOP	Benzotriazol-1-yloxy tris(dimethylamino)- phosphonium hexafluorophosphate
	calc.	calculated
	CBZ, Cbz	Benzyloxycarbonyl
10	DCC	Dicyclohexylcarbodiimide
	DMF	N,N-dimethylformamide
	DMAP	4-Dimethylaminopyridine
	EDC	1-(3-dimethylaminopropyl)-3-ethylcarbodi-imide hydrochloride
15	EI-MS	Electron ion-mass spectroscopy
	Et	ethyl
	eq.	equivalent(s)
	FAB-MS	Fast atom bombardment-mass spectroscopy
	HOBT, HOBt	Hydroxybenztriazole
20	HPLC	High pressure liquid chromatography
	KHMDS	Potassium bis(trimethylsilyl)amide
	LAH	Lithium aluminum hydride
	LHMDS	Lithium bis(trimethylsilyl)amide
	Me	methyl
25	MF	Molecular formula
	MHz	Megahertz
	MPLC	Medium pressure liquid chromatography
	NMM	N-Methylmorpholine
	NMR	Nuclear Magnetic Resonance
30	Ph	phenyl
	Pr	propyl
	prep.	prepared
	TFA	Trifluoroacetic acid
	THF	Tetrahydrofuran

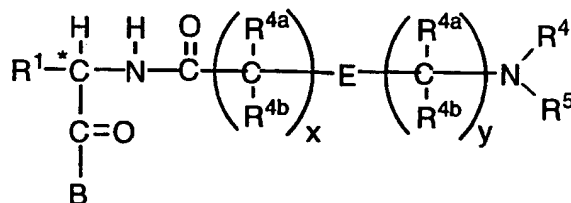
- 30 -

TLC
TMSThin layer chromatography
Tetramethylsilane

The compounds of the instant invention have at least
5 two asymmetric centers when B is:



and both X and Y are groups other than hydrogen and are different from
each other. Additional asymmetric centers may be present depending
upon the nature of the various substituents on the molecule. Each such
10 asymmetric center will independently produce two optical isomers and it
is intended that all of the possible optical isomers and diastereomers in
mixture and as pure or partially purified compounds are included within
the ambit of this invention. In the case of the asymmetric center which
bears the X and Y groups, in most cases, both R- and S- configurations
15 are consistent with useful levels of growth hormone secretagogue
activity. In addition configurations of many of the most preferred
compounds of this invention are



20

Formula I

indicated. When the carbon atom in Formula I bearing an asterisk is of a
defined two diastereomers result according to the absolute configuration
at the carbon atom bearing the X and Y groups. These diastereomers are
25 arbitrarily referred to as diastereomer 1 (d1) and diastereomer 2 (d2) in
this invention and, if desired, their independent syntheses or

- 31 -

chromatographic separations may be achieved as described herein. Their absolute stereochemistry may be determined by the x-ray crystallography of crystalline products or crystalline intermediates which are derivatized, if necessary, with a reagent containing an asymmetric center of known absolute configuration.

The instant compounds are generally isolated in the form of their pharmaceutically acceptable acid addition salts, such as the salts derived from using inorganic and organic acids. Examples of such acids are hydrochloric, nitric, sulfuric, phosphoric, formic, acetic, trifluoroacetic, propionic, maleic, succinic, malonic, methane sulfonic and the like. In addition, certain compounds containing an acidic function such as a carboxy can be isolated in the form of their inorganic salt in which the counterion can be selected from sodium, potassium, lithium, calcium, magnesium and the like, as well as from organic bases.

The preparation of compounds of Formula I of the present invention may be carried out in sequential or convergent synthetic routes. Syntheses detailing the preparation of the compounds of Formula I in a sequential manner are presented in the following reaction schemes.

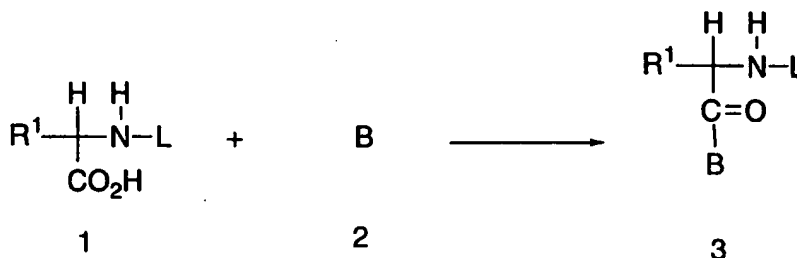
The phrase "standard peptide coupling reaction conditions" is used repeatedly here, and it means coupling a carboxylic acid with an amine using an acid activating agent such as EDC, DCC, and BOP in a inert solvent such as dichloromethane in the presence of a catalyst such as HOBt. The uses of protective groups for amine and carboxylic acid to facilitate the desired reaction and minimize undesired reactions are well documented. Conditions required to remove protecting groups which may be present and can be found in Greene, T, and Wuts, P. G. M., *Protective Groups in Organic Synthesis*, John Wiley & Sons, Inc., New York, NY 1991. CBZ and BOC were used extensively in the synthesis, and their removal conditions are known to those skilled in the art. For example, removal of CBZ groups can be achieved by a number of methods known in the art; for example, catalytic hydrogenation with hydrogen in the presence of a noble metal or its oxide such as palladium on activated carbon in a protic solvent such as ethanol. In cases where catalytic hydrogenation is contraindicated by the presence of other

- 32 -

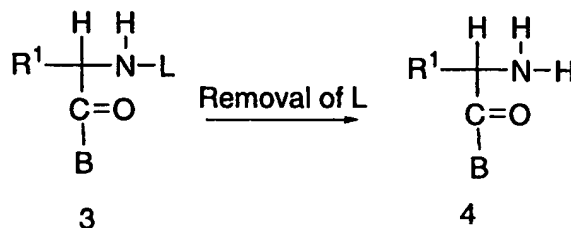
potentially reactive functionality, removal of CBZ groups can also be achieved by treatment with a solution of hydrogen bromide in acetic acid, or by treatment with a mixture of TFA and dimethylsulfide. Removal of BOC protecting groups is carried out in a solvent such as methylene
5 chloride or methanol or ethyl acetate, with a strong acid, such as trifluoroacetic acid or hydrochloric acid or hydrogen chloride gas.

The protected amino acid derivatives 1 are, in many cases, commercially available, where the protecting group L is, for example, BOC or CBZ groups. Other protected amino acid derivatives 1 can be
10 prepared by literature methods (Williams, R. M. *Synthesis of Optically Active α -Amino Acids*, Pergamon Press: Oxford, 1989). Many of the piperidines, pyrrolidines, and hexahydro-1H-azepines of Formula 2 are either commercially available or known in the literature and others can be prepared following literature methods described for analogous
15 compounds. Some of these methods are illustrated in the subsequent schemes. The skills required in carrying out the reaction and purification of the resulting reaction products are known to those in the art. Purification procedures includes crystallization, normal phase or reverse
20 phase chromatography.

- 33 -

SCHEME 1

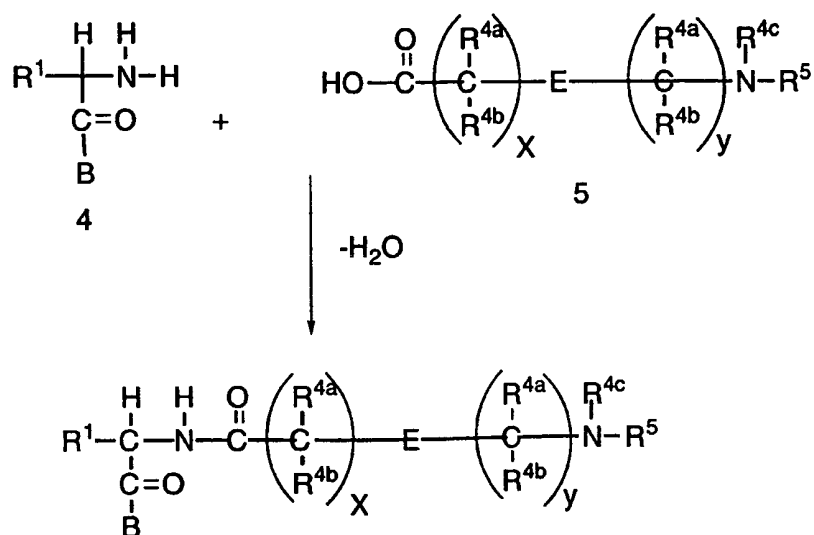
Intermediates of Formula 3 may be synthesized as described in Scheme 1. Coupling of amine of Formula 2, whose preparations are described later if they are not commercially available, to protected amino acids of Formula 1, wherein L is a suitable protecting group, is conveniently carried out under standard peptide coupling conditions.

SCHEME 2

10

Conversion of 3 to intermediate 4 may be carried out as illustrated in Scheme 2 by removal of the protecting group L (CBZ, BOC, etc.)

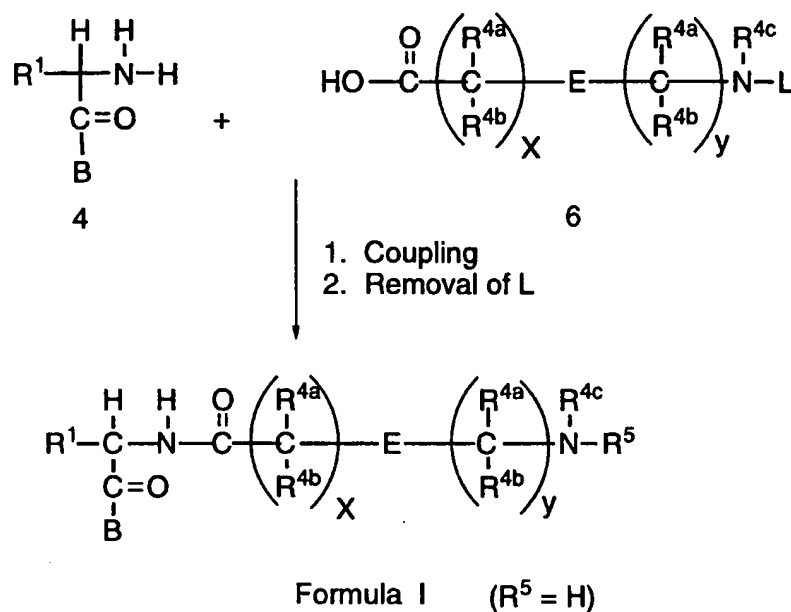
- 34 -

SCHEME 3

Formula I

Intermediates of Formula I may be prepared as shown in Scheme 3 by coupling intermediates of Formula 4 to protected amino acids of Formula 5 under the standard peptide-type coupling reaction conditions. The amino acids 5 are either commercially available or can be synthesized by routine methods.

- 35 -

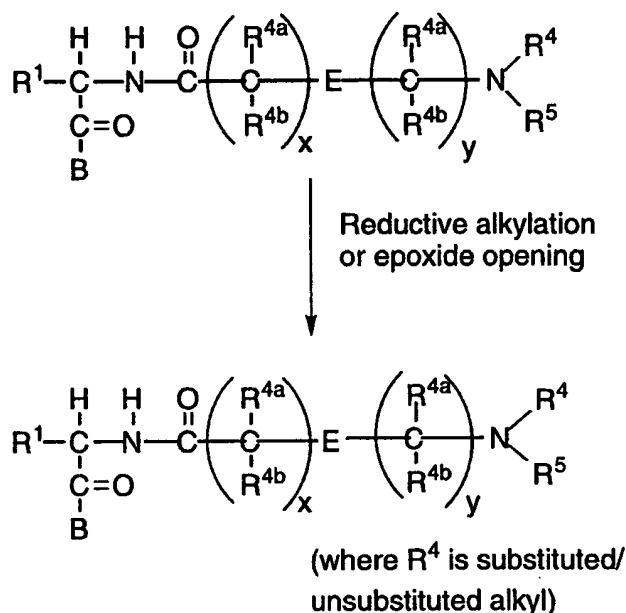
SCHEME 4

5

As shown in Scheme 4, if R⁴ or R⁵ is a hydrogen then the protected amino acids 6 are employed in the coupling reaction wherein L is a protecting group as defined above. The removal of L to afford I can be carried out as noted above.

10

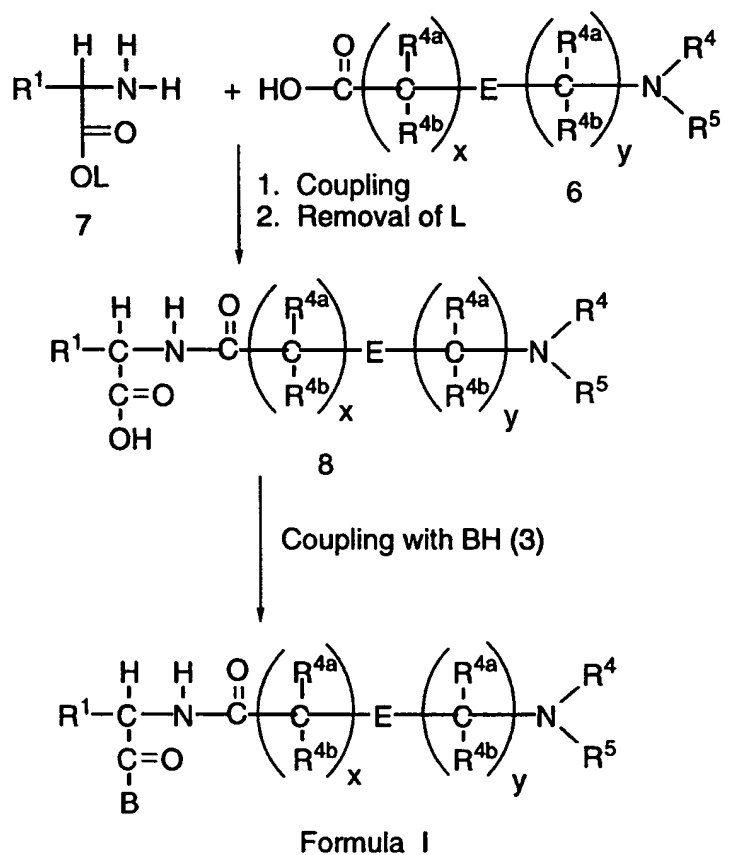
- 36 -

SCHEME 5

- Compounds of Formula I wherein R⁴ and/or R⁵ is a hydrogen may be further elaborated to new Compounds I which are substituted on the amino group as depicted in Scheme 5. Reductive alkylation of I with an aldehyde is carried out under conditions known in the art; for example, by catalytic hydrogenation with hydrogen in the presence of platinum, palladium, or nickel catalysts or with chemical reducing agents such as sodium cyanoborohydride in a protic solvent such as methanol or ethanol in the present of catalytic amount of acid. Alternatively, a similar transformation can be accomplished via an epoxide opening reaction.

- The compounds of general Formula I of the present invention may also be prepared in a convergent manner as described in Scheme 6. Intermediates of Formula 7 can be synthesized by well documented methods in the literature. Elaboration of 7 to compounds of Formula 1 can be accomplished as shown in Scheme 6 by coupling intermediates of Formula 7 to amino acids of Formula 6 under standard peptide coupling reaction conditions.

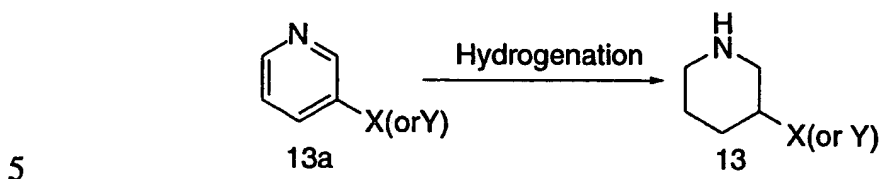
- 37 -

SCHEME 6

- Removal of the protecting group L can be accomplished by well documented methods and amines BH of Formula 2 can be coupled to the corresponding acid under standard peptide-type coupling conditions to give compounds of Formula I. When R⁴ and/or R⁵ is H, substituted alkyl groups may be optionally added to the nitrogen atom as described in Scheme 5.

In the following Schemes preparations of amines BH of Formula 3 are described.

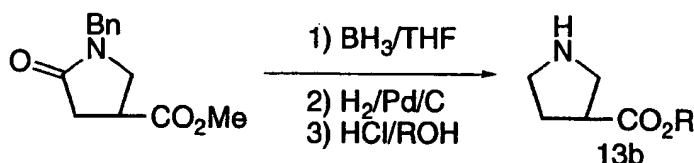
SCHEME 7



3-Monosubstituted piperidines of formula 13 can be prepared by the reduction of pyridine derivatives or their salts by hydrogenation in a suitable organic solvent such as water, acetic acid, alcohol, e.g. ethanol, or their mixture, in the presence of a noble metal catalyst such as platinum or an oxide thereof on a support such as activated carbon, and conveniently at room temperature and atmospheric pressure or under elevated temperature and pressure. 3-Monosubstituted piperidines can also be prepared by modification of the X or Y moiety of the existing 3-monosubstituted piperidines.

15

SCHEME 8

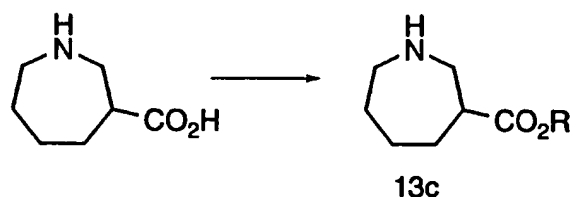


3-Monosubstituted pyrrolidines are commercially available or can be conveniently prepared by literature procedures. Shown in Scheme 8 is an example of the preparation of these compounds via pyrrolidine-3-carboxylic acid ester. The commercially available compound methyl 1-benzyl-4-oxo-3-pyrrolidinecarboxylate is reduced by borane (*J. Chem. Soc.*, 24, 1618-1619). Removal of the benzyl group by catalytic hydrogenolysis followed by ester exchange in an appropriate alcohol medium such as ethyl alcohol in the presence of acid gave the compound 13b. The ester functionality may be further modified through

- 39 -

conventional chemistry to other groups as defined by X. 3-Monosubstituted pyrrolidines may also be prepared by catalytic hydrogenation of 3-substituted pyrroles.

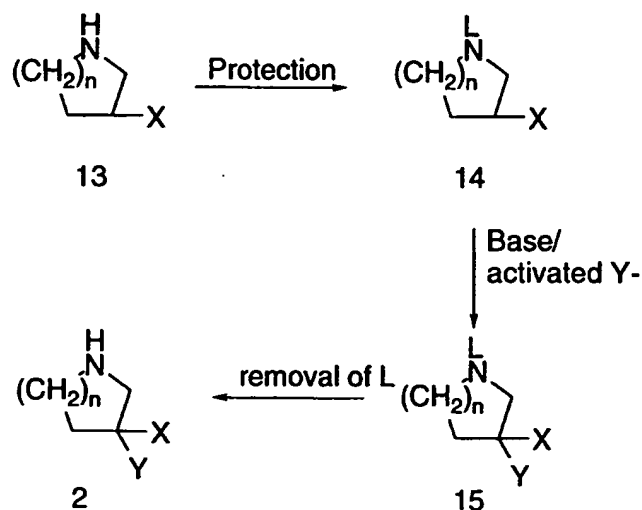
5

SCHEME 9

10

Hexahydro-1H-azepines are commercially available or may be prepared by the literature procedure. Hexahydro-1H-azepine-3-carboxylic acid (Krogsgaard-Larsen, P. et al., *Acta. Chem. Scand.*, B32, 327, (1978)) is esterified in an alcohol solvent in the presence of acid. The ester functionality may be further modified through conventional chemistry to other groups within the definition of X.

15

SCHEME 10

Illustrated in Scheme 10 is a general way to prepare di-substituted piperidines, pyrrolidines, and hexahydro-1H-azepines. Compounds of Formula 13 wherein X is an electron withdrawing group

- 40 -

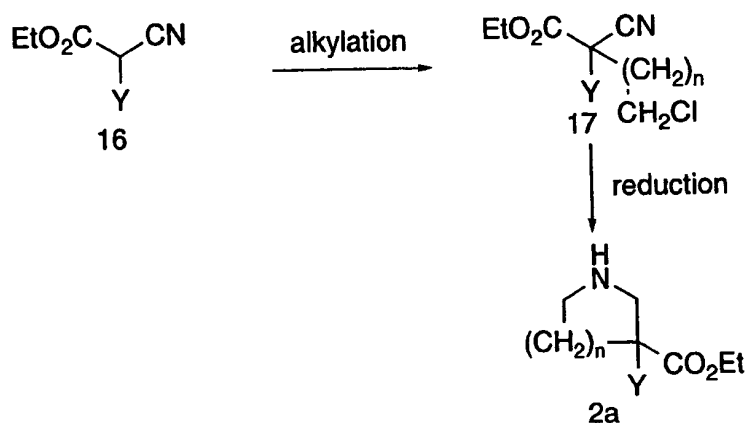
such as -CN, -CO₂R₈, where R₈ is alkyl, aryl, and (C₁-C₄alkyl)aryl are known compounds or may be prepared by methods analogous to those used for the preparation of such known compounds. The secondary amine of compounds of Formula 13 may be first protected by a protecting group L such as BOC and CBZ using the conventional techniques.

5 Introduction of the Y substitution can be achieved by first reacting compounds of Formula 14 with a strong base such as lithium bis(trimethylsilyl)amide, lithium diisopropylamide following by addition of alkylating or acylating reagents such as alkyl halides, aryl alkyl

10 halides, acyl halides, and haloformates in a inert solvent such as THF at temperatures from -100° to room temperature. Thio derivatives where the sulfur is attached directly to an alkyl or an aryl group can be prepared similarly by reacting with a disulfide. The halides used in these reactions are either commercially available or known compounds in the

15 literature or may be prepared by methods analogous to those used for the preparation of known compounds. The protecting group L in compounds of formula 15 may be removed with conventional chemistry to give compounds of Formula 2.

20

SCHEME 11

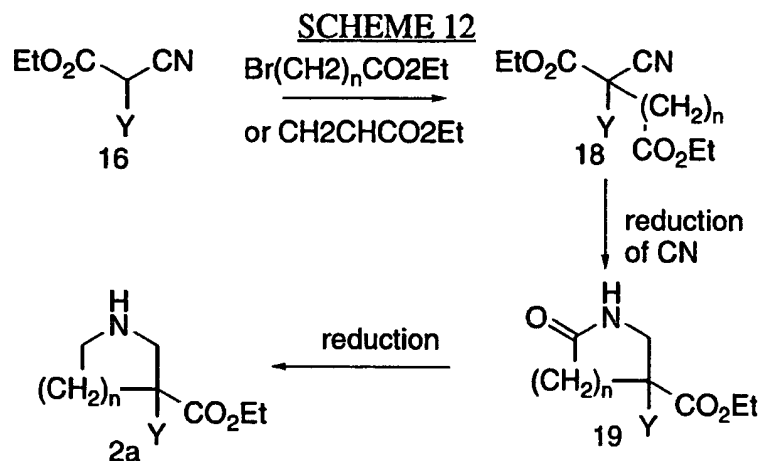
Alternative ways of preparing compounds of Formula 2 include construction of the ring itself (Jacoby, R. L. et al, J. Med. Chem., 17, 453-455, (1974)). Alkylation of the cyanoacetates of general formula

25 16, which are commercially available or may be prepared from literature

- 41 -

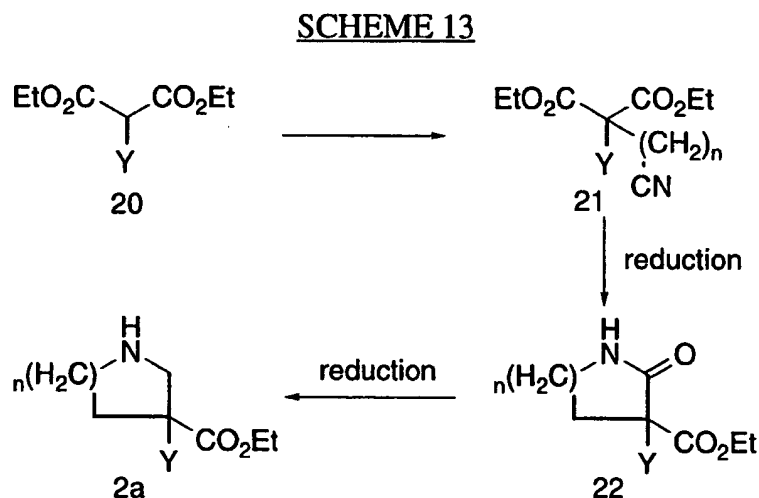
procedures, with alkyl dihalides such as 1-bromo-2-chloroethane or 1-bromo-3-chloropropane yields the chloride 17. Reduction of the nitriles 17 by borane or by hydrogenation using Raney Ni as a catalyst gives the corresponding primary amines, which upon refluxing in ethanol to give
5 compounds of Formula 2a.

- 42 -



Alternatively, the cyanoacetates of general formula 16 may be alkylated with an ethoxycarbonylalkyl bromide or reacted with ethyl acrylate to give compounds of Formula 18. Reduction of the nitriles 18 by borane or by hydrogenation using Raney Ni as a catalyst gives the corresponding primary amines, which upon refluxing in ethanol gives lactam 19. Reduction of the lactam 19 by borane gives compounds of Formula 2a.

10



Alternatively, a malonate of general formula 20 may be alkylated with cyanoalkyl bromide or can be reacted with acrylonitrile to form compounds of formula 21. Reduction of the nitriles 21 by borane or

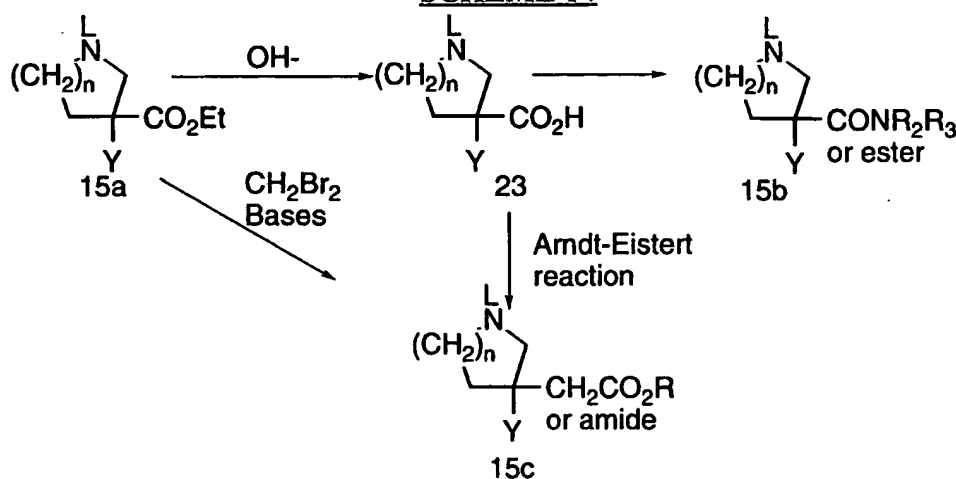
15

- 43 -

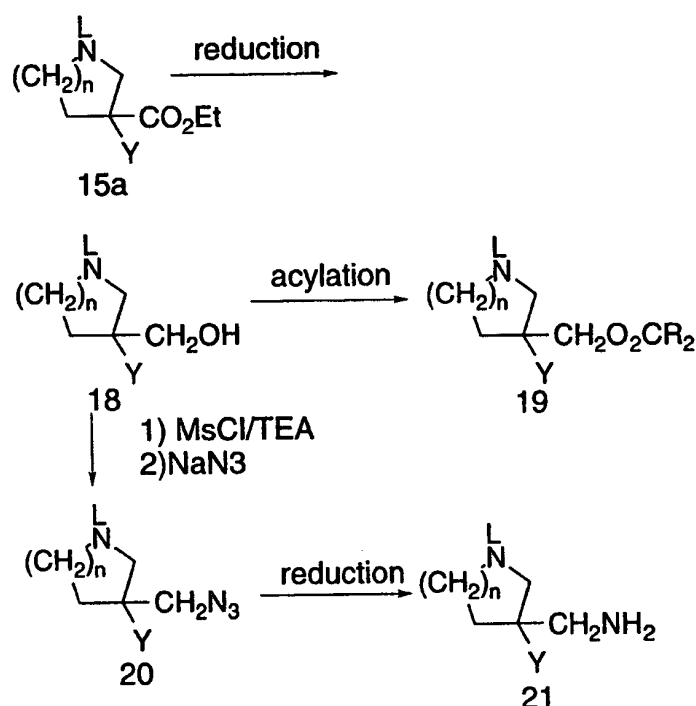
by hydrogenation using Raney Ni as a catalyst gives the corresponding primary amines, which upon refluxing in ethanol gives lactam 22. Reduction of the lactam 22 by borane gives compounds of formula 2a.

5

SCHEME 14

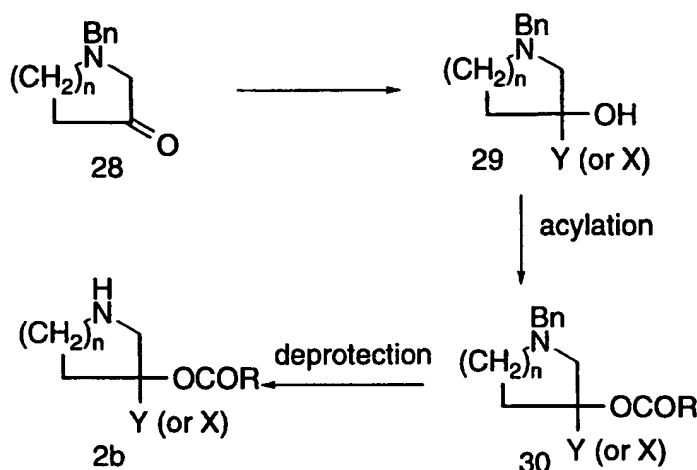


The X, Y functionalities in compounds of general structure 15 may be further elaborated to groups not accessible by direct alkylation. For example in Compound 15 when X = CO_2Et the ester (provided that this is the only ester group in the molecule) can be saponified to the carboxylic acid, which can be further derivatized to amides or other esters. The carboxylic acid can be converted into its next higher homologue, or to a derivative of the homologous acid, such as amide or ester by an Arndt-Eistert reaction. Alternatively, the ester can be directly homologated by the protocol using ynolate anions described by C. J. Kowalski and R. E. Reddy in *J. Org. Chem.*, 57, 7194-7208 (1992). The resulting acid and/or ester may be converted to the next higher homologue, and so on and so forth. The protecting group L may be removed through conventional chemistry.

SCHEME 15

- The ester in 15a may be reduced to an alcohol 18 in a suitable solvent such as THF or ether with a reducing agent such as DIBAL-H and conveniently carried out at temperatures from -100°C to 0°C . The alcohol may be acylated to Compound 19 in a suitable solvent such as dichloromethane using an acyl halide or acid anhydride in the presence of a base such as triethyl amine (TEA). The hydroxy group in 18 may also be converted to a good leaving group such as mesylate and displaced by a nucleophile such as cyanide, a thiol or an azide. Reduction of the azide in compounds of Formula 20 to an amine 21 can be achieved by hydrogenation in the presence of a noble metal such as palladium or its oxide or Raney nickel in a protic solvent such as ethanol.
- The nitrile can be reduced to afford the homologous amine. The amine of Formula 21 may be further elaborated to amides, ureas sulfonamides as defined by X through conventional chemistry. The protecting group L may be removed through conventional chemistry.

- 45 -

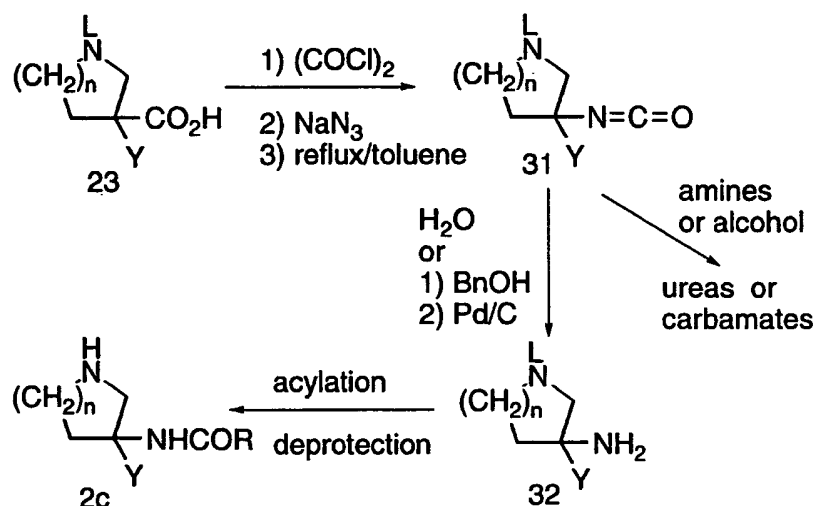
SCHEME 16

5 In cases where oxygen is directly attached to the ring, a convenient method involves the addition reaction by an activated form of an alkyl, aryl, alkylaryl group, such as lithium reagent, Grignard reagents, and the like with a ketone of general formula 28, which is commercially available. Further derivatization of the resulting hydroxy group by

10 acylation, sulfonylation, alkylation, and the like gives compounds as defined by Y or X through conventional chemistry. Removal of the benzyl protective group may be carried out under the usual conditions to give compounds of general formula 2b. Shown in Scheme 16 is a general example of acylations.

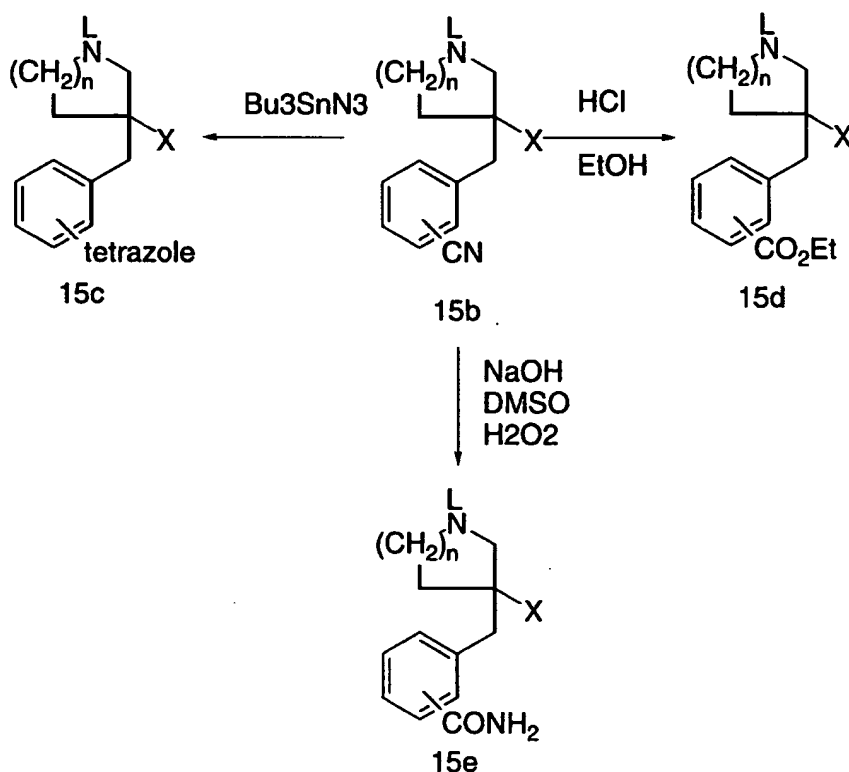
15

- 46 -

SCHEME 17

In cases where a nitrogen-substituted group is directly attached to the ring, a convenient method is to use the Curtius rearrangement on the acid 23 to afford the isocyanate 31. Addition of amines or alcohols give ureas or carbamates respectively which can be deprotected to remove L to give special cases of compounds of formula 2. Conversion of the isocyanate to amine by hydrolysis gives compound 32. Further derivatization of the resulting amine group by acylation, sulfonylation, alkylation, and the like to give compounds as defined by Y or X can be done through conventional chemistry. Removal of the protective group L may be carried out under the usual conditions to give compounds of general formula 2c. Shown in Scheme 17 is a general example of acylations.

- 47 -

SCHEME 18

- For compounds that are not readily obtainable by direct
- 5 alkylation as shown in Scheme 10, modifications of easily obtainable compounds of general formula 15 may be conducted to achieve the desired substitution through conventional chemistry. For example, compounds with Y being hydroxybenzyl may be prepared by demethylation of the corresponding compound wherein Y is
- 10 methoxybenzyl. Similarly, compounds with Y being aminobenzyl may be prepared by reduction of the corresponding compound wherein Y is nitrobenzyl. Shown in Scheme 18 is an example of a procedure that uses nitrile as a starting point for the preparation of compounds with different substitutions. Removal of the protective group L gives compounds of
- 15 general formula 2 as described in Scheme 10.

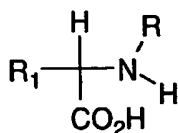
Compounds of the general formula 2 prepared in this way are racemic when X and Y are not identical. Resolution of the two enantiomers can be conveniently achieved by classical crystallization

- 48 -

methods by using a chiral acid such as L- or D-tartaric acid, (+) or (-)-10-camphorsulfonic acid in a suitable solvent such as acetone, water, alcohol, ether, acetate or their mixture. Alternatively, the racemic amine 2 can be reacted with a chiral auxiliary such as (R) or (S)-O-acetylmandelic acid followed by chromatographic separation of the two diastereomers, and removal of the chiral auxiliary by hydrolysis. Alternatively asymmetric alkylation can also be utilized for the synthesis of optically active intermediate by introducing a removable chiral auxiliary in X or in place of L with subsequent chromatographic separation of diastereomers.

In cases where a sulfide is present in the molecule, it may be oxidized to a sulfoxide or to a sulfone with oxidizing agents such as sodium periodate, m-chloroperbenzoic acid or Oxone® in an solvent such as dichloromethane, alcohol or water or their mixtures.

The compounds of the present invention may also be prepared from a variety of substituted natural and unnatural amino acids of formulas 46. The preparation of many of these acids is described in US Patent No. 5,206,237. The preparation of these intermediates in racemic form is accomplished by classical methods familiar to those skilled in the art (Williams, R. M. "Synthesis of Optically Active α -Amino Acids" Pergamon Press: Oxford, 1989; Vol. 7). Several methods exist to resolve (DL)-



46

amino acids. One of the common methods is to resolve amino or carboxyl protected intermediates by crystallization of salts derived from optically active acids or amines. Alternatively, the amino group of carboxyl protected intermediates may be coupled to optically active acids by using chemistry described earlier. Separation of the individual diastereomers either by chromatographic techniques or by crystallization followed by hydrolysis of the chiral amide furnishes resolved amino acids. Similarly, amino protected intermediates may be converted to a

- 49 -

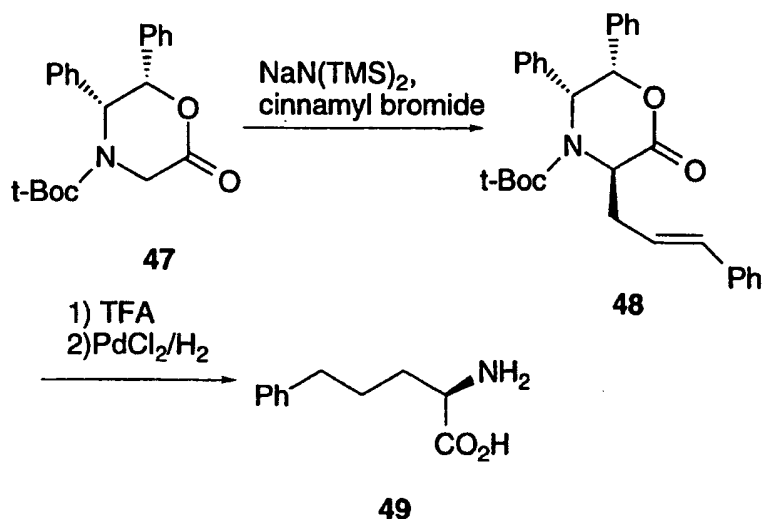
mixture of chiral diastereomeric esters and amides. Separation of the mixture using methods described above and hydrolysis of the individual diastereomers provides (D) and (L) amino acids. Finally, an enzymatic method to resolve N-acetyl derivatives of (DL)-amino acids has been
5 reported by Whitesides and coworkers in *J. Am. Chem. Soc.* 1989, 111, 6354-6364.

When it is desirable to synthesize these intermediates in optically pure form, established methods include: (1) asymmetric electrophilic amination of chiral enolates (*J. Am. Chem. Soc.* 1986, 108,
10 6394-6395, 6395-6397, and 6397-6399), (2) asymmetric nucleophilic amination of optically active carbonyl derivatives, (*J. Am. Chem. Soc.* 1992, 114, 1906; *Tetrahedron Lett.* 1987, 28, 32), (3) diastereoselective alkylation of chiral glycine enolate synthons (*J. Am. Chem. Soc.* 1991, 113, 9276; *J. Org. Chem.* 1989, 54, 3916), (4) diastereoselective
15 nucleophilic addition to a chiral electrophilic glycinate synthon (*J. Am. Chem. Soc.* 1986, 108, 1103), (5) asymmetric hydrogenation of prochiral dehydroamino acid derivatives ("Asymmetric Synthesis, Chiral Catalysis; Morrison, J. D., Ed; Academic Press: Orlando, FL, 1985; Vol 5), and (6) enzymatic syntheses (*Angew. Chem. Int. Ed. Engl.* 1978, 17, 176).

20

- 50 -

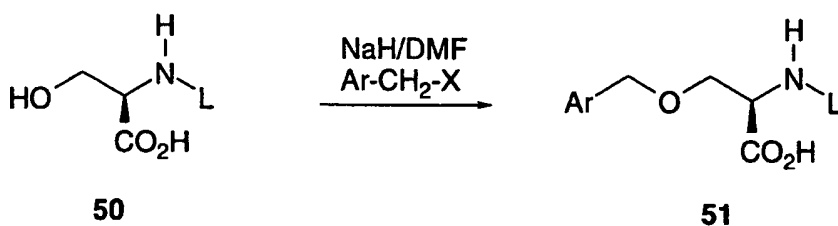
SCHEME 19



For example, alkylation of the enolate of diphenyloxazinone 47 (*J. Am. Chem. Soc.* 1991, 113, 9276) with cinnamyl bromide in the presence of sodium bis(trimethylsilyl)amide proceeds smoothly to afford 48 which is converted into the desired (D)-2-amino-5-phenylpentanoic acid 49 by removing the N-t-butyloxycarbonyl group with trifluoroacetic acid and hydrogenation over a PdCl_2 catalyst (Scheme 19).

10

SCHEME 20



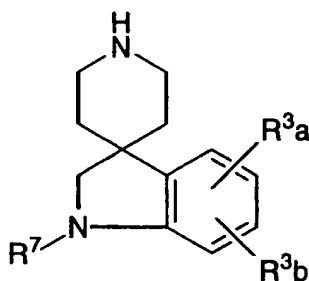
Intermediates of formula 46 which are O-benzyl-(D)-serine derivatives 51 are conveniently prepared from suitably substituted benzyl halides and N-protected-(D)-serine 50. The protecting group L is conveniently a BOC or a CBZ group. Benzylation of 64 can be achieved by a number of methods well known in the literature including deprotonation with two equivalents of sodium hydride in an inert solvent

- 51 -

such as DMF followed by treatment with one equivalent of a variety of benzyl halides (*Synthesis* 1989, 36) as shown in Scheme 20.

The O-alkyl-(D)-serine derivatives may also be prepared using an alkylation protocol. Other methods that could be utilized to
5 prepare (D)-serine derivatives of formula 51 include the acid catalyzed benzylation of carboxyl protected intermediates derived from 50 with reagents of formula $\text{ArCH}_2\text{OC}(=\text{NH})\text{CCl}_3$ (O. Yonemitsu *et al.*, *Chem. Pharm. Bull.* 1988, 36, 4244). Alternatively, alkylation of the chiral glycine enolates (*J. Am. Chem. Soc.* 1991, *113*, 9276; *J. Org. Chem.*
10 1989, *54*, 3916) with $\text{ArCH}_2\text{OCH}_2\text{X}$ where X is a leaving group affords 51. In addition D,L-O-aryl(alkyl)serines may be prepared and resolved by methods described above.

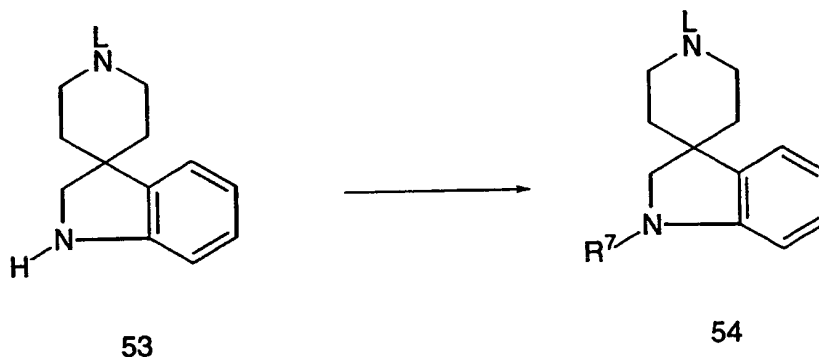
The spiro piperidines of formula 52 may be prepared by a number of methods, including the syntheses described below.



15

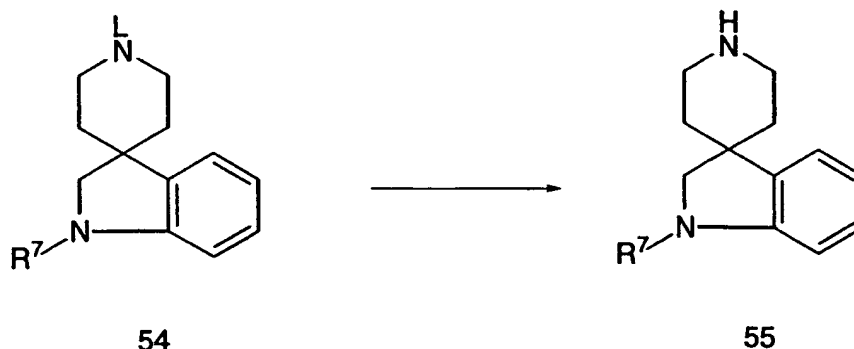
52

- 52 -

SCHEME 21

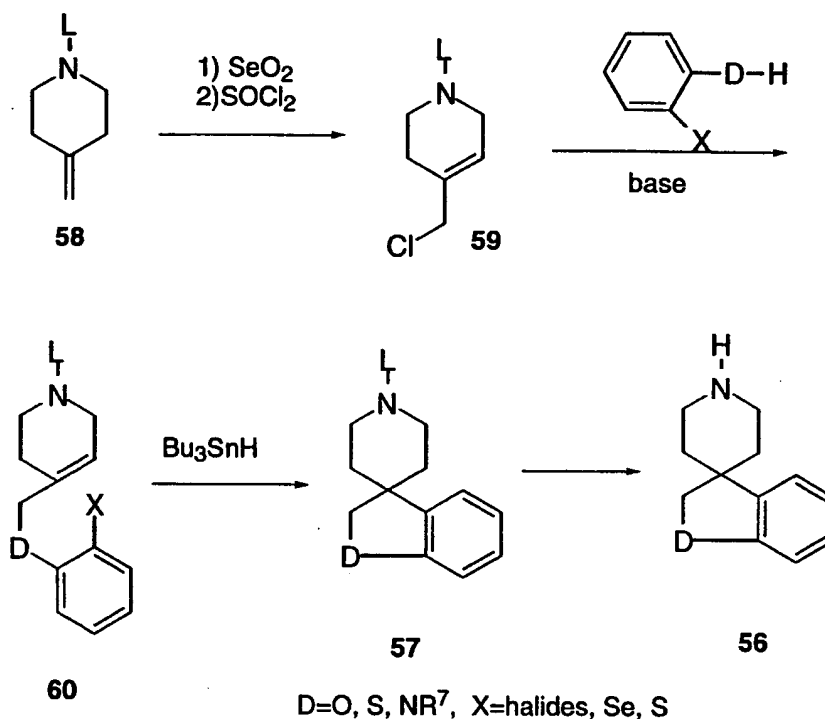
As shown in Scheme 21, the spiro piperidine of formula 43, wherein L is a defined protecting group, is synthesized by methods that are known in the literature (for example H. Ong et al *J. Med. Chem.* 1983, 23, 981-986). The indoline nitrogen of 54, wherein L is a protecting group such as methyl or benzyl, can be reacted by with a variety of electrophiles to yield spiro piperidines of formula 54, wherein R⁹ can be a variety of functionalities. Compound 54 can be reacted with, for example, isocyanates in an inert solvent like dichloromethane to yield urea derivatives, chloroformates in an inert solvent such as dichloromethane to yield carbamates, acid chlorides, anhydrides, or acyl imidazoles to generate amides, sulfonyl chlorides to generate sulfonamides, sulfamyl chlorides to yield sulfamides. Also, the indoline nitrogen of 53 can be reductively alkylated with aldehydes with conditions known in the art. When the aldehyde used in the reductive amination reaction is a protected glyoxylic acid of structure HCOCOOM, wherein M is a defined protecting group, M can be removed from the product and further derivatized. Alternatively, 53 can be reacted with epoxides to produce 53, wherein R⁹ is β -hydroxy-substituted alkyl or arylalkyl groups. The indoline 53 can also be transformed to compounds of formula 54, wherein R⁹ = phenyl or substituted phenyl, heteroaryl or substituted heteroaryl, by carrying out the reacting 53 with a fluoro phenyl or fluoro heteroaryl reagent. This chemistry is detailed by H. Ong et al *J. Med. Chem.* 1983, 23, 981-986.

- 53 -

SCHEME 22

The spiro piperidine intermediate 54 (L = Me or Bn), wherein R⁷ is hydrogen or most of the derivatives described above, can be demethylated or debenzylated to produce 55, wherein R⁹ is hydrogen or most of the derivatives described above, as shown in Scheme 22. For compounds of formula 54, wherein L = Me, demethylation can be carried out by a number methods familiar those skilled in the art. For example, demethylation of 54 be accomplished by reacting it with cyanogen bromide and potassium carbonate in an inert solvent solvent such as dichloromethane to yield a cyanamide which can reduced to give 55 by treatment with lithium aluminum hydride in refluxing tetrahydrofuran, refluxing strong acid like aqueous hydrochloric acid, or with Grignard reagents like methyl magnesium bromide. Alternatively, demethylation of 54 can be effected with the ACE-Cl method as described in R. Olofson et al. *J. Org. Chem.* 1984, 49, 2795 and references therein. For intermediates of formula 54, wherein L = Bn, removal of benzyl group can be accomplished by reductive methods including hydrogenation in the presence of platinum or palladium catalyst in a protic solvent like methanol. Alternatively, debenzylation of 54, L = Bn, can be effected with the ACE-Cl method as described in R. Olofson et al. *J. Org. Chem.* 1984, 49, 2795 and references therein.

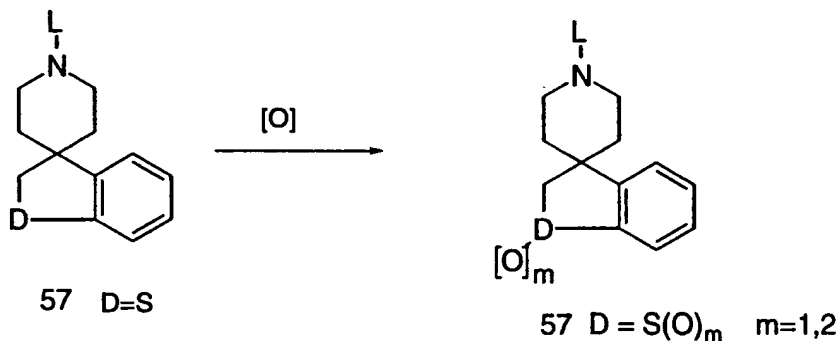
- 54 -

SCHEME 23

- The spiro heterocyclic compounds of formula 56 can be prepared by a number of methods, including the syntheses as described in Scheme 23. Allylic oxidation of the protected piperidine 58 is accomplished by classical methods familiar to those skilled in the art (Rabjohn, *N. Org. React.* 1976, 24, 261). The resulting allylic alcohol is treated with thionyl chloride in an inert solvent such as benzene to provide the corresponding chloride 59. When D=O or S, the alkylation is carried out in DMF or acetone as solvent with potassium carbonate as a base, and when D=NR⁷ (R⁷=H, alkyl, aryl, acyl, sulfonyl, carbamate) the reaction is carried out with sodium hydride as a base in an inert solvent such as THF to afford the cyclization precursor 60. When L is a defined protecting group, compound 60 can be cyclized by a number methods familiar to those skilled in the art. For example, cyclization of 60 can be accomplished by reaction with tributyltin hydride (Curran, *D. P. Synthesis* 1988, 417 and 489) in an inert solvent such as benzene to yield

- 55 -

57. Alternatively, compound 57 (D=NR₉) can be prepared by the method shown in Schemes 24 and 25.

SCHEME 24

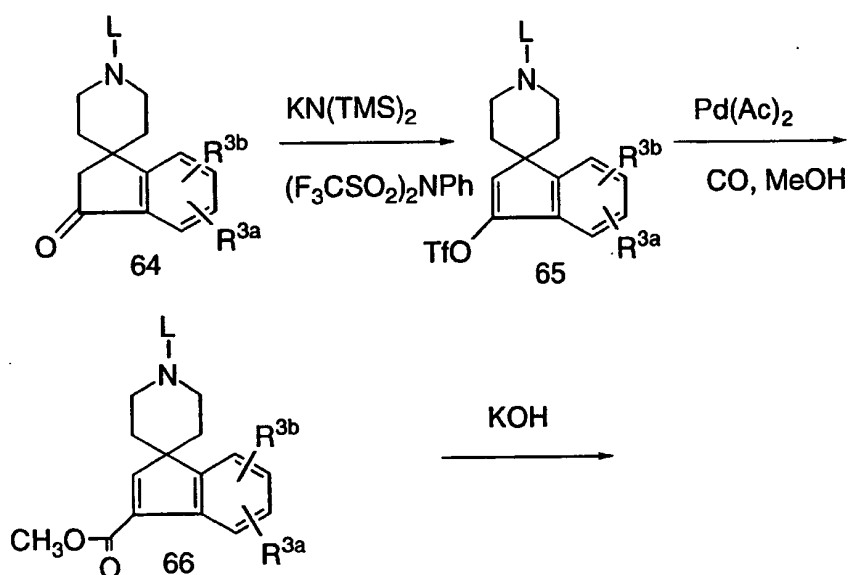
5

As shown in Scheme 24, when D=S, compound 57 can be oxidized to the sulfoxide 57 (n=1) and the sulfone 57 (n=2) by many oxidizing agents. For example, sodium periodate is often used for the synthesis of sulfoxides and Oxone is used for the synthesis of sulfones.

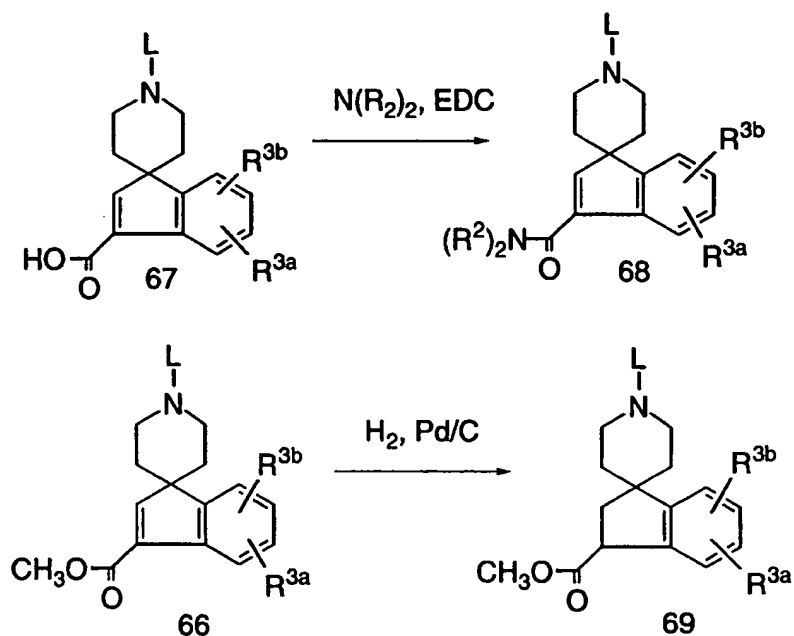
- 10 Removal of the protecting group provides the amine 56 which then can be incorporated into a growth hormone secretagogue via the chemistry detailed in Scheme 1 and 8 shown above which utilize generic intermediate 2.

- 56 -

Compounds of formula I wherein R^4 and R^5 are each hydrogen can be further elaborated by reductive alkylation with an aldehyde by the aforementioned procedures or by alkylations such as by reaction with various epoxides. The products, obtained as hydrochloride or trifluoroacetate salts, are conveniently purified by reverse phase high performance liquid chromatography (HPLC) or by recrystallization.

SCHEME 26

- 57 -



Homologation of the spiroindanone 64 provides easy access to spiroindanyl intermediates containing acid and ester groups. This chemistry is described in Scheme 26. Treatment of 64 with a base in an inert solvent such as THF followed by the addition of a triflating agent provides the enol triflate. Carboxylation of the enol triflate according to the procedure of Cacchi, S. *Tetrahedron Letters*, 1985, 1109-1112 provides the ester 66. The protecting group can then be removed as described above and the resulting amine can be incorporated into the subject compound via the chemistry depicted in Schemes 1 and 8. A compound containing an acid function is readily available via saponification of the ester group as the final step of the synthesis.

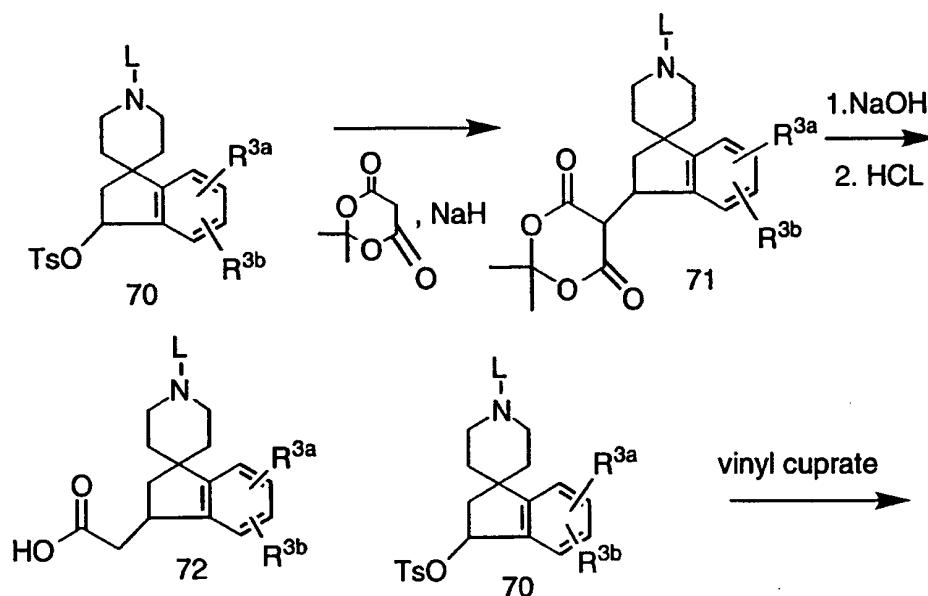
Saponification of the ester of 66 provides an acid which can be conveniently derivatized as for example reaction with an amine in the presence of a coupling agent such as EDC gives amides which can then be incorporated into final compounds following the chemistry detailed in Schemes 1 and 8.

Hydrogenation of 66 using a palladium catalyst in an inert solvent provides the saturated compounds which can then either be derivatized as above or carried on to the final products via the chemistry

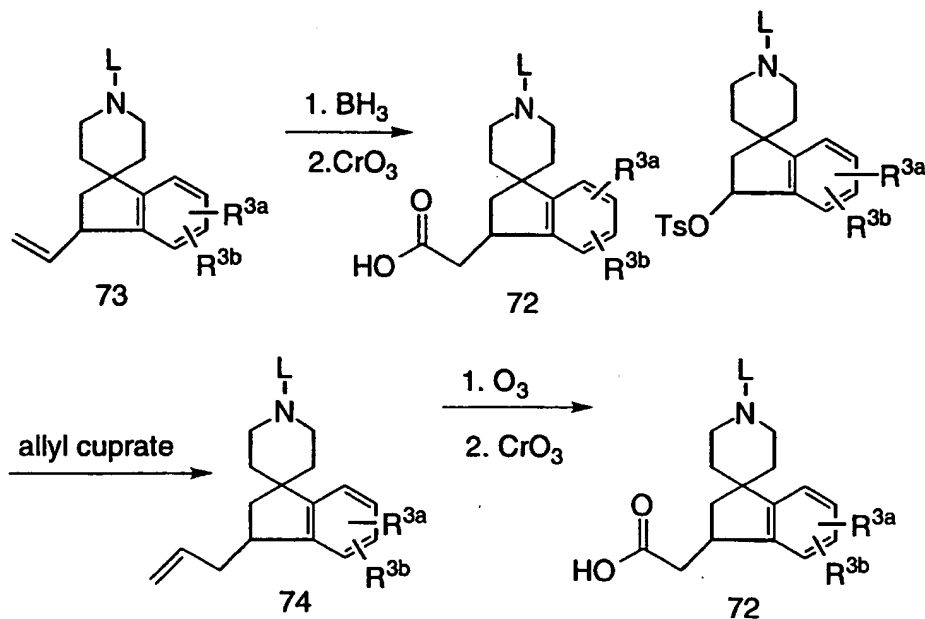
- 58 -

described in Schemes 1 and 8. The ester may also be reduced to a primary alcohol with LAH and to a aldehyde with DIBALH. Reductive alkylation of the aldehyde with ammonium acetate and sodium cyanoborohydride affords an amino methyl analog. These hydroxymethyl and aminomethyl analogs may then be further reacted to afford additional growth hormone secretagogues of the general formula I. Chiral acids are available by a variety of methods known to those skilled in the art including asymmetric catalytic hydrogenation and resolution of a pair of diastereomeric salts formed by reaction with a chiral amine such as D or L α -methylbenzylamine. The absolute stereochemistry can be determined in a number of ways including X-ray crystallography of a suitable crystalline derivative.

Spiroindane intermediates, for incorporation into growth hormone secretagogues, can be further elaborated in the benzylic position by the chemistry detailed in the following schemes.

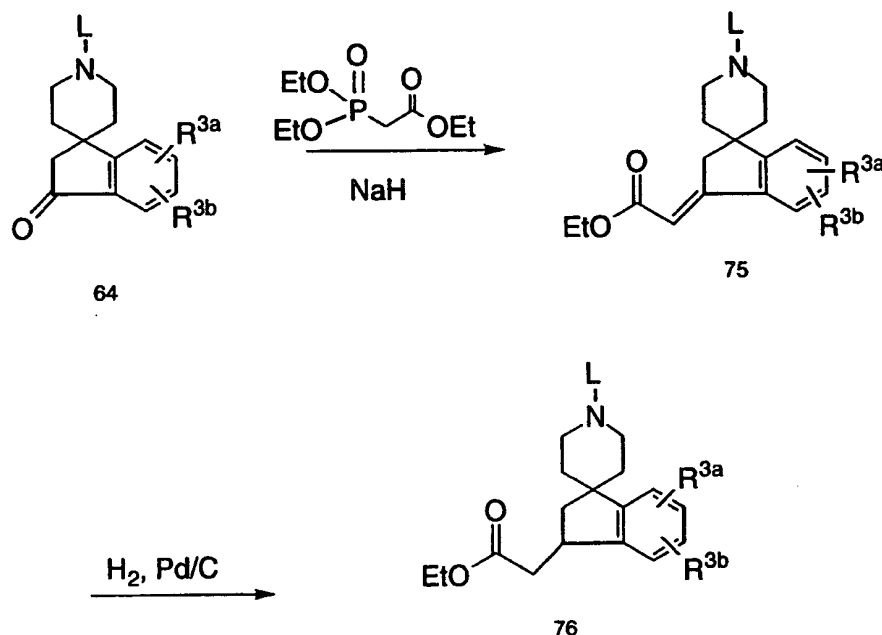
SCHEME 27

- 59 -



As depicted in Scheme 27, homologs of ester 69 can be conveniently prepared by a variety of methods known to those skilled in the art including the displacement of an activated alcohol such as tosylate 70 by a malonate nucleophile followed by decarboxylation or a cuprate reaction followed by the adjustment of the chain length or oxidation state as appropriate.

- 60 -

SCHEME 28

Alternatively the reaction of spiroindanone 64 with Wittig or Emmons reagents also provides access to homologs of ester 69. The chemistry is described in Scheme 28. Treatment of triethylphosphonoacetate with a base in an inert solvent such as THF followed by the addition of ketone 64 provides the unsaturated ester 75. Hydrogenation of 75 using a palladium catalyst in an inert solvent provides the saturated ester 76. The protecting group can then be removed as described above and the resulting amine can be incorporated into a final compound via the chemistry described in Schemes 1 and 8. A secretagogue containing an acid function can be obtained via saponification of the ester function as the final step of the synthesis.

Chiral esters and acids are available by a variety of methods known to those skilled in the art including asymmetric catalytic hydrogenation, chromatographic resolution of a pair of diastereomers, and via crystallization of salts formed from chiral amines such as D or L- α -methylbenzylamine. The absolute stereochemistry can be determined in

- 61 -

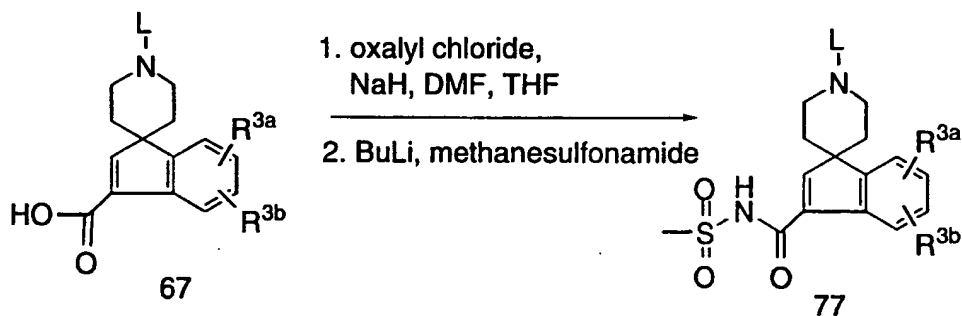
a number of ways including X-ray crystallography of a suitable crystalline derivative.

The ester can be reduced to an alcohol by treatment with LAH and to an aldehyde with DIBALH. Reductive alkylation of the aldehyde with ammonium acetate and sodium cyanoborohydride affords an amino methyl analog. These hydroxymethyl and aminomethyl analogs may then be further reacted to afford additional growth hormone secretagogues of the general formula 1.

Saponification of ester 44 provides an acid which can be conveniently derivatized as for example reaction with an amine in the presence of a coupling reagent such as EDC gives amides which can be incorporated into a secretagogue as detailed in Schemes 1 and 8.

Homologation of ester 44 is possible using a variety of methods known to those skilled in the art including the method described in J. Org. Chem. 1992, 57 7194-7208.

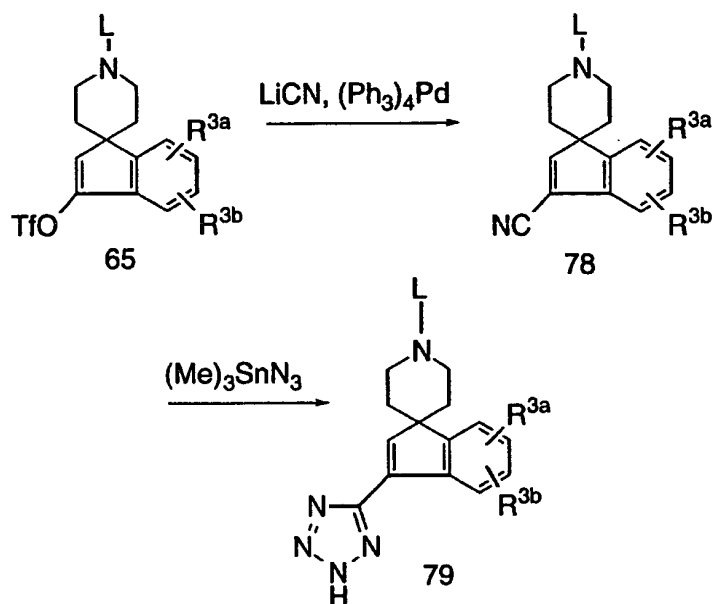
SCHEME 29



As shown in Scheme 29, a variety of acid equivalents can also be incorporated into the spiroindane intermediates for example acylsulfonamides are readily available from acids such as 67 and 72. Treatment of the spiroindane acid with a base in an inert solvent such as THF followed by the addition of oxalyl chloride provides an acid chloride which is then treated with a sodium salt of a sulfonamide. The protecting group can then be removed using chemistry described above and the resulting amine can be incorporated into a final compound using chemistry depicted in Schemes 1 and 8.

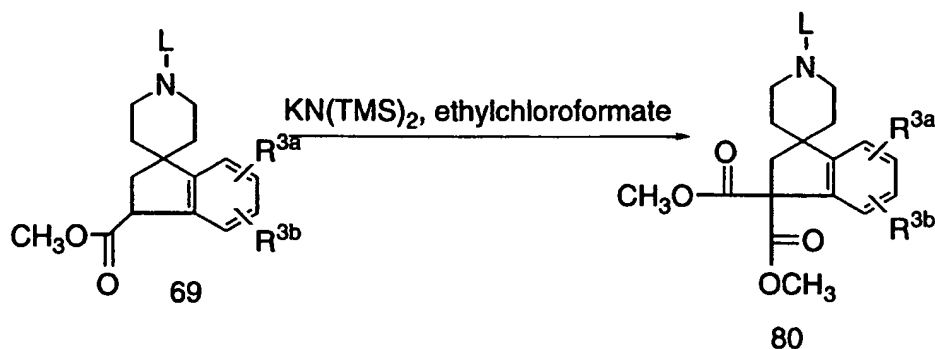
- 62 -

SCHEME 30



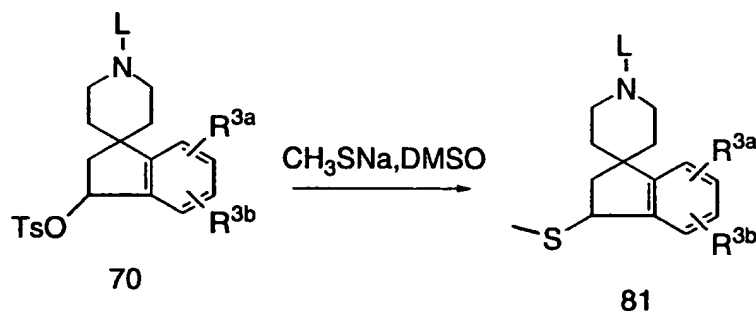
As shown in Scheme 30, tetrazole spiroindane intermediates
5 are available from nitriles of both the shorter and longer homolog series.
For example the reaction of enol triflate 65 with a cyanide anion and a
palladium catalyst in the presence of an inert solvent such as toluene
provides the unsaturated nitrile which can be converted into the tetrazole
by reaction with trimethylstannyl azide in an inert solvent at elevated
10 temperatures. Reduction of the indene double bond in 78 and 79 with
catalysts such as Pd/C in ethanol affords the corresponding saturated
analogs.

- 63 -

SCHEME 31

As shown in Scheme 31, esters such as 69 can be conveniently acylated or alkylated next to the ester function by treatment with a variety of bases and alkylating or acylating agents. For example reaction of 69 with potassium bis(trimethyl-silylamide) in an inert solvent such as THF followed by the addition of ethyl chloroformate provides 80 in good yield. Removal of the protecting group and incorporation into the subject compounds can be accomplished as described above.

10

SCHEME 32

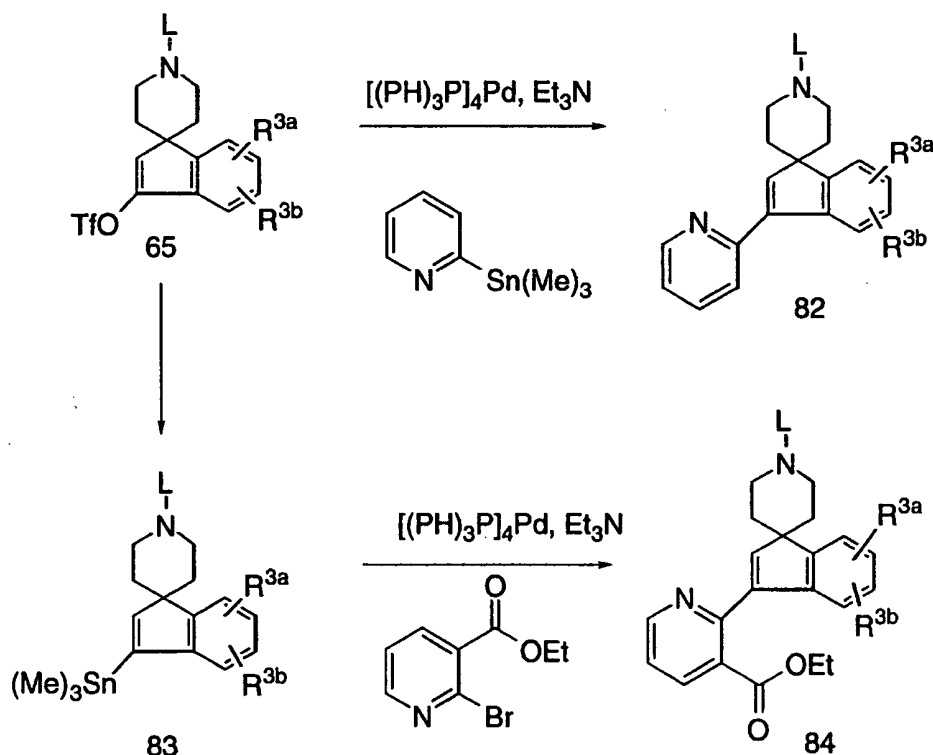
As shown in Scheme 32, further substitution at the benzylic position of the spiroindanes is readily carried out via the tosylate of the alcohol. Displacement of the tosylate with a variety of nucleophiles is possible. For example treatment of tosylate 70 with sodium thiomethoxide in DMSO provides the sulfide 81. The protecting group can be removed as above and the resulting amine can be incorporated into

15

- 64 -

the final compound employing chemistry described in Schemes 1 and 8. Alternatively the sulfide can be oxidized to the sulfoxide or sulfone by treatment with the appropriate oxidizing agent prior to deprotection or as the final step in the synthesis.

5

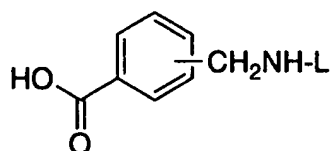
SCHEME 33

As shown in Scheme 33, the incorporation of aryl and heteroaryl groups into the benzylic position of spiroindanes is most conveniently carried out via the enol triflate 65. Palladium catalyzed reaction of the enol triflate with a variety of aryl or heteroaryl stannanes in an inert solvent such as toluene provides the desired intermediates. For example 2-trimethylstannyl-pyridine reacts with 65 in the presence of a catalytic amount of tetrakis(triphenylphosphene)palladium in toluene at reflux to give the coupled product 82. Alternatively the enol triflate 65 can be converted into the vinyl stannane 83 by reaction with hexamethylditin and a palladium catalyst in an inert solvent such as

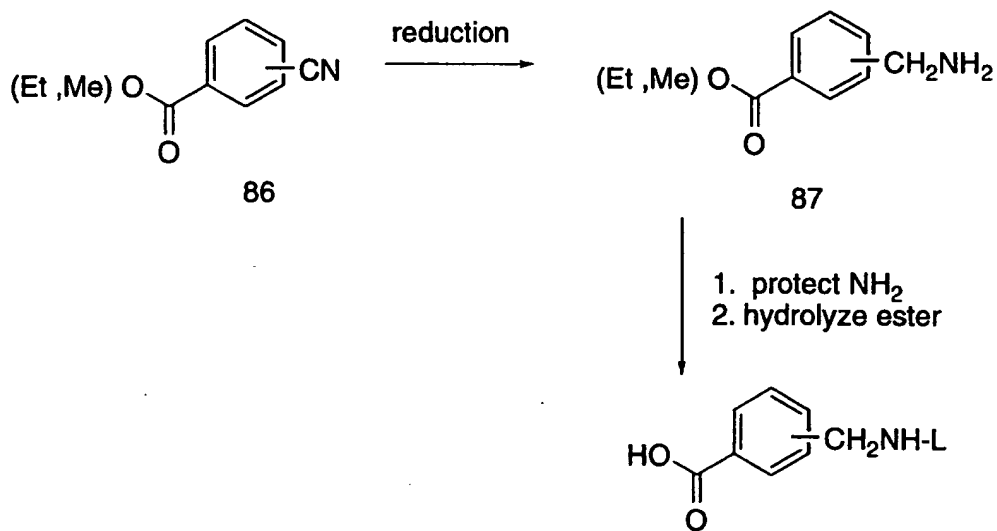
- 65 -

toluene. The vinyl stannane can then be coupled with a variety of aryl or hetero aryl bromides or triflates, for example coupling to 2-bromo-3-carbo-methoxypyridine provides 84. The protecting group L can be removed from the coupled products using chemistry described above and the resulting amine can be included in the final compound as described in Schemes 1 and 8.

In the following Schemes 34-36 syntheses of amino acids of Formula 6 are described. Various methods are well documented in the art to prepare protected amino acids of formula 85.



85

SCHEME 34

85

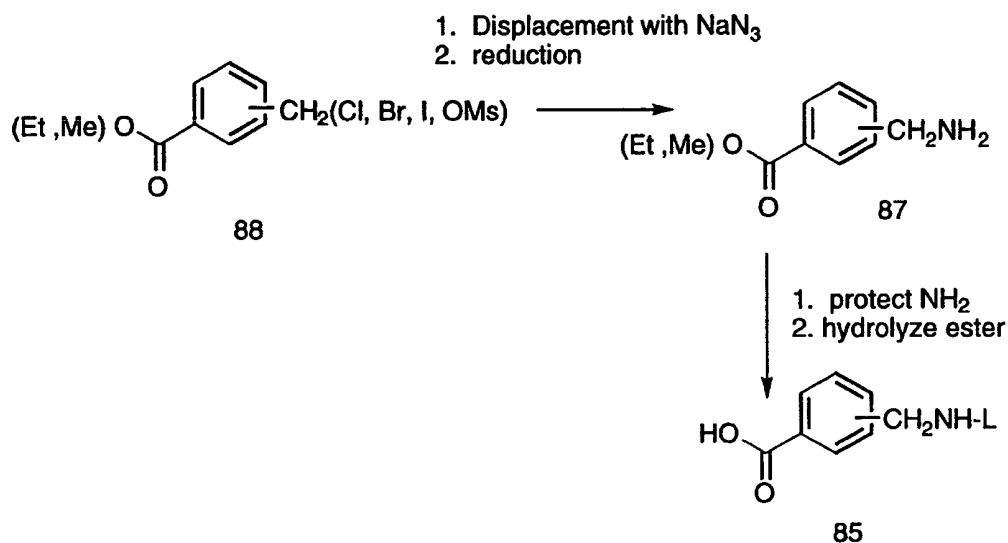
As shown in Scheme 34, benzoic acids esters of formula 86 are reduced with Raney nickel in ethanol in the presence of ammonia to provide the corresponding benzylamine derivative 87. The amino group

- 66 -

is protected as its Boc or CBZ derivative and the ester group is hydrolyzed to give protected amino acids of formula 85.

SCHEME 35

5

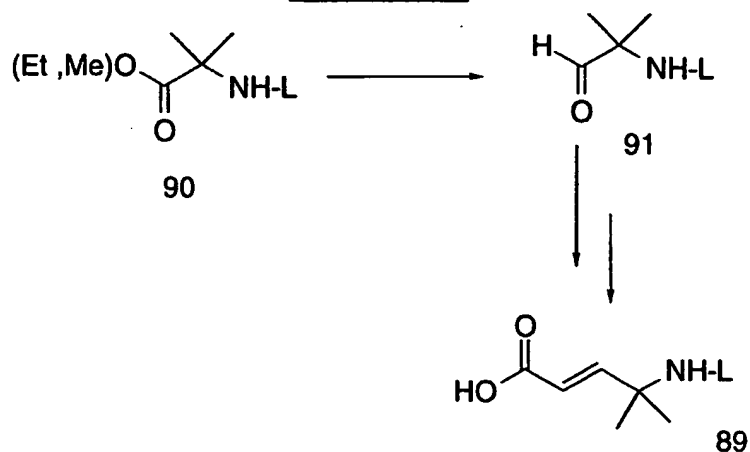


As shown in Scheme 35, other methods of the synthesis of 85 originate from benzyl halides of formula 88. The halide is displaced with sodium azide usually in a polar aprotic solvent such as DMF or DMSO to give the corresponding azide that is reduced with triphenylphosphine in THF-water to give the amine derivative that is converted to acids of formula 85 as described above.

10

- 67 -

SCHEME 36



Olefinic amino acids of formula 89 may be prepared as shown in Scheme 36. The Boc-aminoisobutyric acid methyl ester 90 is reduced to the corresponding aldehyde derivative 91 with the use of diisobutylaluminum hydride in an aprotic solvent such as THF or dichloromethane. Alternatively, the commercially available acid of 90 may be reduced with diborane to the alcohol and reduced up to the aldehyde 91 by using Swern oxidation protocol. A Horner-Emmons condensation of 91 with triethylphosphonoacetate by using a base like potassium t-butoxide in an aprotic solvent provides the corresponding unsaturated ester that can be hydrolyzed under standard conditions to protected amino acid of formula 89.

In some cases the order of carrying out the foregoing reaction schemes may be varied to facilitate the reaction or to avoid unwanted reaction products.

The utility of the compounds of the present invention as growth hormone secretagogues may be demonstrated by methodology known in the art, such as an assay disclosed by Smith, et al., *Science*, 260, 1640-1643 (1993) (see text of Figure 2 therein). In particular, all of the compounds prepared in the following examples had activity as growth hormone secretagogues in the aforementioned assay. Such a result is indicative of the intrinsic activity of the present compounds as growth hormone secretagogues.

- 68 -

The growth hormone releasing compounds of Formula I are useful *in vitro* as unique tools for understanding how growth hormone secretion is regulated at the pituitary level. This includes use in the evaluation of many factors thought or known to influence growth hormone secretion such as age, sex, nutritional factors, glucose, amino acids, fatty acids, as well as fasting and non-fasting states. In addition, the compounds of this invention can be used in the evaluation of how other hormones modify growth hormone releasing activity. For example, it has already been established that somatostatin inhibits growth hormone release. Other hormones that are important and in need of study as to their effect on growth hormone release include the gonadal hormones, e.g., testosterone, estradiol, and progesterone; the adrenal hormones, e.g., cortisol and other corticoids, epinephrine and norepinephrine; the pancreatic and gastrointestinal hormones, e.g., insulin, glucagon, gastrin, secretin; the vasoactive peptides, e.g., bombesin, the neurokinins; and the thyroid hormones, e.g., thyroxine and triiodothyronine. The compounds of Formula I can also be employed to investigate the possible negative or positive feedback effects of some of the pituitary hormones, e.g., growth hormone and endorphin peptides, on the pituitary to modify growth hormone release. Of particular scientific importance is the use of these compounds to elucidate the subcellular mechanisms mediating the release of growth hormone.

The compounds of Formula I can be administered to animals, including man, to release growth hormone *in vivo*. For example, the compounds can be administered to commercially important animals such as swine, cattle, sheep and the like to accelerate and increase their rate and extent of growth, to improve feed efficiency and to increase milk production in such animals. In addition, these compounds can be administered to humans *in vivo* as a diagnostic tool to directly determine whether the pituitary is capable of releasing growth hormone. For example, the compounds of Formula I can be administered *in vivo* to children. Serum samples taken before and after such administration can be assayed for growth hormone. Comparison of the amounts of growth hormone in each of these samples would be a means for directly

- 69 -

determining the ability of the patient's pituitary to release growth hormone.

Accordingly, the present invention includes within its scope pharmaceutical compositions comprising, as an active ingredient, at least one of the compounds of Formula I in association with a pharmaceutical carrier or diluent. Optionally, the active ingredient of the pharmaceutical compositions can comprise an anabolic agent in addition to at least one of the compounds of Formula I or another composition which exhibits a different activity, e.g., an antibiotic growth permittant or an agent to treat osteoporosis or in combination with a corticosteroid to minimize the latter's catabolic side effects or with other pharmaceutically active materials wherein the combination enhances efficacy and minimizes side effects.

Growth promoting and anabolic agents include, but are not limited to, TRH, diethylstilbesterol, amino acids, estrogens, β -agonists, theophylline, anabolic steroids, enkephalins, E series prostaglandins, retinoic acid, compounds disclosed in U.S. Patent No. 3,239,345, e.g., zeranol, and compounds disclosed in U.S. Patent No. 4,036,979, e.g., sulbenox. or peptides disclosed in U.S. Patent No. 4,411,890.

A still further use of the compounds of this invention is in combination with other growth hormone secretagogues such as the growth hormone releasing peptides GHRP-6, GHRP-1 as described in U.S. Patent Nos. 4,411,890 and publications WO 89/07110, WO 89/07111 and B-HT920 as well as hexarelin and GHRP-2 as described in WO 93/04081 or growth hormone releasing hormone (GHRH, also designated GRF) and its analogs or growth hormone and its analogs or somatomedins including IGF-1 and IGF-2 or α -adrenergic agonists such as clonidine or serotonin 5HTID agonists such as sumatriptan or agents which inhibit somatostatin or its release such as physostigmine and pyridostigmine. In particular, the compounds of this invention may be used in combination with growth hormone releasing factor, an analog of growth hormone releasing factor, IGF-1, or IGF-2. For example, a compound of the present invention may be used in combination with IGF-1 for the treatment or prevention of obesity. In addition, a

- 70 -

compound of this invention may be employed in conjunction with retinoic acid to improve the condition of musculature and skin that results from intrinsic aging.

5 The present invention is further directed to a method for the manufacture of a medicament for stimulating the release of growth hormone in humans and animals comprising combining a compound of the present invention with a pharmaceutical carrier or diluent.

10 As is well known to those skilled in the art, the known and potential uses of growth hormone are varied and multitudinous. Thus, the administration of the compounds of this invention for purposes of stimulating the release of endogenous growth hormone can have the same effects or uses as growth hormone itself. These varied uses may be summarized as follows: stimulating growth hormone release in elderly humans; treating growth hormone deficient adults; prevention of
15 catabolic side effects of glucocorticoids; treatment of osteoporosis; stimulation of the immune system, acceleration of wound healing; accelerating bone fracture repair; treatment of growth retardation; treating acute or chronic renal failure or insufficiency; treatment of physiological short stature, including growth hormone deficient children; treating short
20 stature associated with chronic illness; treating obesity and growth retardation associated with obesity; treating growth retardation associated with Prader-Willi syndrome and Turner's syndrome; accelerating the recovery and reducing hospitalization of burn patients or following major surgery such as gastrointestinal surgery; treatment of intrauterine growth
25 retardation, and skeletal dysplasia; treatment of hypercortisonism and Cushing's syndrome; treatment of peripheral neuropathies; replacement of growth hormone in stressed patients; treatment of osteochondrodysplasias, Noonans syndrome, sleep disorders, schizophrenia, depression, Alzheimer's disease, delayed wound healing, and psychosocial
30 deprivation; treatment of pulmonary dysfunction and ventilator dependency; prevention or treatment of congestive heart failure, improving pulmonary function, restoring systolic and diastolic function, increasing myocardial contractility, decreasing peripheral total vascular resistance, diminishing or preventing loss of body weight and enhancing

- 71 -

recovery following congestive heart failure; increasing appetite; attenuation of protein catabolic response after a major operation; treating malabsorption syndromes; reducing cachexia and protein loss due to chronic illness such as cancer or AIDS; accelerating weight gain and protein accretion in patients on TPN (total parenteral nutrition); treatment of hyperinsulinemia including nesidioblastosis; adjuvant treatment for ovulation induction and to prevent and treat gastric and duodenal ulcers; stimulation of thymic development and prevention of the age-related decline of thymic function; adjunctive therapy for patients on chronic hemodialysis; treatment of immunosuppressed patients and to enhance antibody response following vaccination; increasing the total lymphocyte count of a human, in particular, increasing the T4/T8-cell ratio in a human with a depressed T4/T8-cell ratio resulting, for example, from infection, such as bacterial or viral infection, especially infection with the human immunodeficiency virus; treatment of syndromes manifested by non-restorative sleep and musculoskeletal pain, including fibromyalgia syndrome or chronic fatigue syndrome; improvement in muscle strength, mobility, maintenance of skin thickness, metabolic homeostasis, renal homeostasis in the frail elderly; stimulation of osteoblasts, bone remodelling, and cartilage growth; prevention and treatment of congestive heart failure; protection of cardiac structure and/or cardiac function; enhancing of recovery of a mammal following congestive heart failure; enhancing and/or improving sleep quality as well as the prevention and treatment of sleep disturbances; enhancing or improving sleep quality by increasing sleep efficiency and augmenting sleep maintenance; prevention and treatment of mood disorders, in particular depression; improving mood and subjective well being in a subject suffering from depression; stimulation of the immune system in companion animals and treatment of disorders of aging in companion animals; growth promotant in livestock; and stimulation of wool growth in sheep. Further, the instant compounds are useful for increasing feed efficiency, promoting growth, increasing milk production and improving the carcass quality of livestock. Likewise, the instant compounds are useful in a method of treatment of diseases or conditions which are

- 72 -

benefited by the anabolic effects of enhanced growth hormone levels that comprises the administration of an instant compound.

In particular, the instant compounds are useful in the prevention or treatment of a condition selected from the group consisting of: osteoporosis; catabolic illness; immune deficiency, including that in
5 individuals with a depressed T4/T8 cell ratio; bone fracture, including hip fracture; musculoskeletal impairment in the elderly; growth hormone deficiency in adults or in children; short stature in children; obesity; sleep disorders; cachexia and protein loss due to chronic illness such as AIDS
10 or cancer; and treating patients recovering from major surgery, wounds or burns, in a patient in need thereof.

In addition, the instant compounds may be useful in the treatment of illnesses induced or facilitated by corticotropin releasing factor or stress- and anxiety-related disorders, including stress-induced
15 depression and headache, abdominal bowel syndrome, immune suppression, HIV infections, Alzheimer's disease, gastrointestinal disease, anorexia nervosa, hemorrhagic stress, drug and alcohol withdrawal symptoms, drug addiction, and fertility problems.

It will be known to those skilled on the art that there are
20 numerous compounds now being used in an effort to treat the diseases or therapeutic indications enumerated above. Combinations of these therapeutic agents some of which have also been mentioned above with the growth hormone secretagogues of this invention will bring additional, complementary, and often synergistic properties to enhance the growth
25 promotant, anabolic and desirable properties of these various therapeutic agents. In these combinations, the therapeutic agents and the growth hormone secretagogues of this invention may be independently present in dose ranges from one one-hundredth to one times the dose levels which are effective when these compounds and secretagogues are used singly.

30 Combined therapy to inhibit bone resorption, prevent osteoporosis and enhance the healing of bone fractures can be illustrated by combinations of bisphosphonates and the growth hormone secretagogues of this invention. The use of bisphosphonates for these utilities has been reviewed, for example, by Hamdy, N.A.T. Role of

- 73 -

Bisphosphonates in Metabolic Bone Diseases. *Trends in Endocrinol. Metab.*, , 4, 19-25 (1993). Bisphosphonates with these utilities include alendronate, tiludronate, dimethyl - APD, risedronate, etidronate, YM-175, clodronate, pamidronate, and BM-210995. According to their
5 potency, oral daily dosage levels of the bisphosphonate of between 0.1 mg and 5 g and daily dosage levels of the growth hormone secretagogues of this invention of between 0.01 mg/kg to 20 mg/kg of body weight are administered to patients to obtain effective treatment of osteoporosis.

In the case of alendronate daily oral dosage levels of 0.1 mg
10 to 50 mg are combined for effective osteoporosis therapy with 0.01 mg/kg to 20 mg/kg of the growth hormone secretagogues of this invention.

Osteoporosis and other bone disorders may also be treated with compounds of this invention in combination with calcitonin,
15 estrogens, raloxifene and calcium supplements such as calcium citrate or calcium carbonate.

Anabolic effects especially in the treatment of geriatric male patients are obtained with compounds of this invention in combination with anabolic steroids such as oxymetholone, methyltestosterone,
20 fluoxymesterone and stanozolol.

The compounds of this invention can be administered by oral, parenteral (e.g., intramuscular, intraperitoneal, intravenous or subcutaneous injection, or implant), nasal, vaginal, rectal, sublingual, or topical routes of administration and can be formulated in dosage forms
25 appropriate for each route of administration.

Solid dosage forms for oral administration include capsules, tablets, pills, powders and granules. In such solid dosage forms, the active compound is admixed with at least one inert pharmaceutically acceptable carrier such as sucrose, lactose, or starch. Such dosage forms
30 can also comprise, as is normal practice, additional substances other than inert diluents, e.g., lubricating agents such as magnesium stearate. In the case of capsules, tablets and pills, the dosage forms may also comprise buffering agents. Tablets and pills can additionally be prepared with enteric coatings.

- 74 -

Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs containing inert diluents commonly used in the art, such as water. Besides such inert diluents, compositions can also include
5 adjuvants, such as wetting agents, emulsifying and suspending agents, and sweetening, flavoring, and perfuming agents.

Preparations according to this invention for parenteral administration include sterile aqueous or non-aqueous solutions, suspensions, or emulsions. Examples of non-aqueous solvents or
10 vehicles are propylene glycol, polyethylene glycol, vegetable oils, such as olive oil and corn oil, gelatin, and injectable organic esters such as ethyl oleate. Such dosage forms may also contain adjuvants such as preserving, wetting, emulsifying, and dispersing agents. They may be sterilized by, for example, filtration through a bacteria-retaining filter, by
15 incorporating sterilizing agents into the compositions, by irradiating the compositions, or by heating the compositions. They can also be manufactured in the form of sterile solid compositions which can be dissolved in sterile water, or some other sterile injectable medium immediately before use.

20 Compositions for rectal or vaginal administration are preferably suppositories which may contain, in addition to the active substance, excipients such as cocoa butter or a suppository wax.

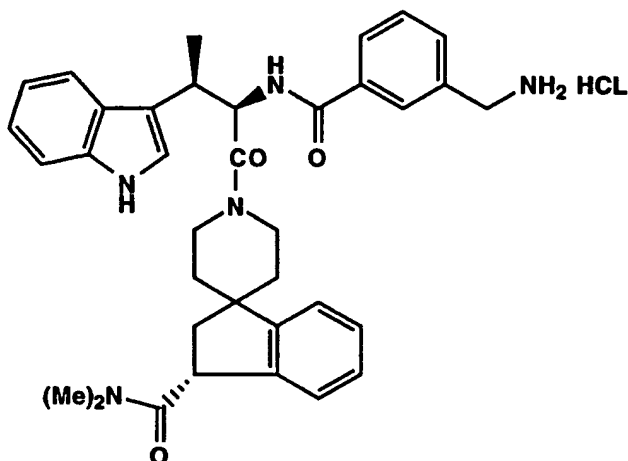
Compositions for nasal or sublingual administration are also prepared with standard excipients well known in the art.

25 The dosage of active ingredient in the compositions of this invention may be varied; however, it is necessary that the amount of the active ingredient be such that a suitable dosage form is obtained. The selected dosage depends upon the desired therapeutic effect, on the route of administration, and on the duration of the treatment. Generally,
30 dosage levels of between 0.0001 to 10 mg/kg. of body weight daily are administered to patients and animals, e.g., mammals, to obtain effective release of growth hormone. Preferably, the dosage level will be about 0.001 to about 25 mg/kg per day; more preferably about 0.01 to about 10 mg/kg per day.

The following examples are provided for the purpose of further illustration only and are not intended to be limitations on the disclosed invention.

5

EXAMPLE 1



Step A: N-Acetyl-*Threo*-(2R,3S)-β-methyltryptophan R-(+)-α-methylbenzyl amine salt

10 Racemic β -methyltryptophan was prepared by the method of Snyder and Matteson (*J. Am. Chem. Soc.* 1957, 79, 2217.) Isomer A (100g) was suspended in 1.25L of 90/10 acetone water at 20°C and 50 mL of R-(+)- α -methylbenzylamine was added in one portion. The suspension cleared briefly before a thick white suspension formed which

15 quickly turned to a solid mass. After aging overnight, an additional 500 mL of acetone was added to facilitate agitation and filtration. The suspension was filtered and the cake washed with 500 mL of acetone and sucked to a damp cake. The solid was suspended in 2.5 L of 90/10 acetone /water and heated to boiling on a steam bath. The white slurry

20 was allowed to cool to 20°C overnight. The product was collected by filtration, washed with acetone and dried yielding 39.1 g of the title compound. $\alpha = + 9.1^\circ$ (c=1, MeOH) Stereochemical assignments were

- 76 -

made by comparison to published compounds: *J. Org. Chem.* 1994, 59, 4239 and *J. Org. Chem.* 1995, 60, 4978.

Step B: N-Acetyl-Threo-(2S,3R)- β -methyltryptophan S-(-)- α -methylbenzyl amine salt

5 The mother liquors from the Step A were combined and concentrated to ca. 1 L and 400 mL of 1 N HCl was added. The resulting suspension was stirred for 1 hr initially at 20°C then at 0°C. The product was filtered and washed with water until the filtrate was neutral. The
10 product was sucked to a damp cake weighing 79 g. The solid was suspended in 1L of 95% acetone/water and 40 mL of S-(-)- α -methylbenzylamine was added followed by 1 L of 90% acetone/water. After a few minutes a solid mass formed. An additional 500 mL of acetone was added and the mixture heated on a steam bath for ca. 0.5 hr.
15 This was then allowed to stand at 20°C overnight. The product was collected by filtration, washed with 500 mL of acetone, and sucked to a damp cake. The product was suspended in 2 L of 95% acetone/water and heated on a steam bath to boiling. The white suspension was allowed to cool to 20°C overnight. The product was collected by filtration, washed
20 with 500 mL of acetone and dried yielding 54 g. $\alpha = -9.0^\circ$ (c=1, MeOH).

Step C: N-Acetyl-Erythro (2R,3R)- β -methyltryptophan R-(+)- α -methylbenzyl amine salt

25 170g of Isomer B (see ref. in Step A) which was a brittle foam containing ethyl acetate was dissolved in 2.5 L of ethyl acetate containing 100 mL of ethanol. To this was added 60 mL of R-(+)- α -methylbenzylamine. After 10 min, an additional 2L of ethyl acetate was added and the resulting thick suspension was aged at 20°C for 3 days.
30 The product was collected by filtration, washed with ethyl acetate and and sucked to a damp cake. The salt was reslurried four times with hot ethyl acetate containing 2% water (1 x 2.5 L, 2 x 6 L, and 1 x 8 L). The yield of dried product was 43.2 g of salt. $\alpha = -19.6^\circ$ (c=1, MeOH).

- 77 -

Step D: N-Acetyl-Erythro (2S,3S)- β -methyltryptophan S-(-)- α -methylbenzyl amine salt

The mother liquors from the Step C were combined and concentrated to *ca.* 2 L and washed twice with 500 mL 1 N HCl. The washes were back extracted once with ethyl acetate, and the combined ethyl acetate extracts washed twice with brine. The solution was diluted to 6 L with ethyl acetate and 60 mL of S-(-)- α -methylbenzylamine was added. After 10 min the resulting suspension was heated to boiling. The suspension was allowed to cool to ambient temperature with stirring overnight. The product was collected by filtration washed with ethyl acetate and and sucked to a damp cake. The salt was suspended in 6 L of ethyl acetate and suspension was heated to boiling. The suspension was allowed to cool to ambient temperature with stirring overnight. The product was collected by filtration washed with ethyl acetate and dried. The yield of dried product was 65.8 g of salt. $\alpha = +19.7^\circ$ ($c=1$, MeOH).

Step E: N-acetyl-threo-(2S,3R)- β -Methyltryptophan

The salt from Step B (53 g) was stirred with 400 mL 1 N HCl at 20°C for 20 min. The suspension was filtered and the cake washed with water until the filtrate was neutral. The wet cake was used directly for the next reaction. A sample was dried affording the title compound. $\alpha = -26.4^\circ$ ($c=1$, MeOH).

Step F: threo-(2S,3R)- β -Methyltryptophan

The wet cake from Step E was suspended in with 400 mL of 1 N HCl and refluxed for 12 hours. The solution was cooled to 20°C, and half of the solution was used for Step G. The title compound isolated by adjusting the pH to 7.0 with sodium hydroxide, cooling the resulting suspension to 0°C, filtering, washing the cake with water and drying. $\alpha = -29.3^\circ$ ($c=0.9$, H₂O).

Step G: N-t-BOC-threo-(2S,3R)- β -methyltryptophan

The pH of the aqueous solution from Step F was adjusted to 7 with sodium hydroxide and cooled to 0°C. 20 g of potassium

- 78 -

carbonate, 19 g of di-*t*-butyldicarbonate, and 150 mL of THF were added. The mixture was allowed to warm slowly to ambient temperature overnight. The reaction was extracted twice with ether, the aqueous acidified with 2 N HCl and extracted twice with ethyl acetate. The combined ethyl acetate extracts were washed with brine, dried with MgSO₄, filtered and concentrated affording 21.2 g of the title compound.

Step H: N-Acetyl-*threo*-(2R,3S)- β -methyltryptophan

The title compound was prepared following the procedure of Step E. $\alpha = +26.6^\circ$ (c=1, MeOH).

Step I: *threo*-(2R,3S)- β -Methyltryptophan

The title compound was prepared following the procedure of Step F. $\alpha = +30.6^\circ$ (c=0.9, H₂O).

Step J: N-*t*-BOC-*threo*-(2R,3S)- β -Methyltryptophan

The title compound was prepared following the procedure of Step G.

Step K: N-Acetyl-*Erythro* (2S,3S)- β -methyltryptophan

The salt from GRK example 4 (65 g) was stirred with 250 mL 1 N HCl and 1.5 L of ethyl acetate at ambient temperature for 5 min. The layers were partitioned and the ethyl acetate layer was washed with 1N HCl, H₂O and brine, dried with MgSO₄, filtered and concentrated to afford the title compound as a brittle foam.

- 79 -

Step L: Erythro (2S,3S)- β -methyltryptophan

The product from Step K was suspended in with 500 mL of 2 N HCl and refluxed for 4 hours. The solution was cooled to 20°C, and half of the solution was used for Step M. The title compound isolated as a
5 foam by concentrating the solution *in vacuo*.

Step M: N-t-BOC-Erythro (2S,3S)- β -methyltryptophan

The pH of the aqueous solution from Step F was adjusted to 7 with sodium hydroxide and cooled to 0°C. 24 g of potassium
10 carbonate, 22 g of di-t-butyldicarbonate, and 150 mL of THF were added. The mixture was allowed to warm slowly to ambient temperature overnight. The reaction was extracted twice with ether. The aqueous acidified with 2 N HCl and extracted twice with ethyl acetate. The combined ethyl acetate extracts were washed with brine, dried with
15 MgSO₄ filtered and concentrated. The solid was redissolved in ether, and the ether removed *in vacuo* while flushing with hexanes. The resulting slurry was filtered and dried affording 20.1 g of the title compound.

20 Step N: N-Acetyl-threo-(2R,3R)- β -methyltryptophan

The title compound was prepared following the procedure of Step K. $\alpha = 0$ (c=1, MeOH).

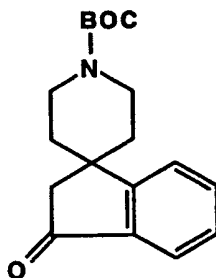
Step O: threo-(2R,3R)- β -methyltryptophan

25 The title compound was prepared following the procedure of Step L. $\alpha = 0$ (c=0.9, H₂O).

Step P: N-t-BOC-threo-(2R,3R)- β -methyltryptophan

30 Step M. The title compound was prepared following the procedure of

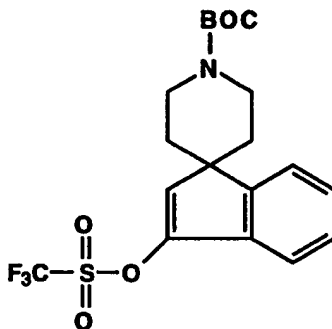
- 80 -

Step Q:

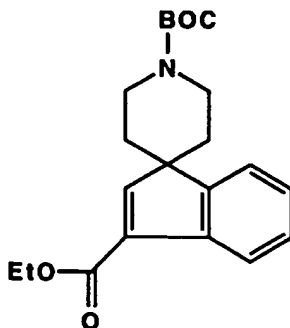
To a solution of 51.0 g (0.177 mol) of 1'-(t-butyloxy-carbonyl)spiro[1H-indene-1,4'-piperidine] [prepared by the method of Chambers, *et al*, J. Med. Chem. , 1992, 35, 2036] in 200 ml of THF was added 430 ml (0.5 M in THF, 0.213 mol) of 9-BBN. The reaction mixture was heated at 70°C until TLC analysis indicated that the starting material was consumed (18 hrs). The solution was concentrated to ~300 ml and then cooled to 0°C and quenched with methanol (10 ml). 4 N Sodium hydroxide (213 ml) and 30 % hydrogen peroxide (108 ml) were added via an addition funnel over 45 minutes. The reaction mixture was stirred for 3.5 hours and then solid sodium sulfite was added until starch paper indicated that no more peroxides were present. The reaction mixture was extracted with ethyl acetate (4 X 1 vol). The ethyl acetate layer was dried over magnesium sulfate filtered and concentrated. The crude material was dissolved in dichloromethane (300 ml) and the solution was cooled to 0°C then celite (25 g) and PCC (57 g) were added in five portions over 20 minutes. The reaction mixture was warmed to room temperature and stirred overnight. The solution was then diluted with ether and filtered through a pad of a mixture of celite and florisil. Purification by flash chromatography (silica gel, hexane/ethyl acetate, 5:1 to 3:1) gave 58.6 g of the title compound. ¹H NMR (200 MHz, CDCl₃): 7.75-7.60 (m, 2H), 7.50-7.44 (m, 2H), 4.30-4.15 (m, 2H), 2.85 (dt, 2H), 2.63 (s, 2H), 1.98 (dt, 2H), 1.53-1.40 (m, 2H), 1.49 (s, 9H).

25

- 81 -

Step R:

- Potassium bis(trimethylsilyl)amide (127.5 ml, 0.5 M) was added to the ketone (16.0 g, 53 mmol) in THF (200 mL) at 0 °C. The reaction mixture was stirred for one hour and then N-phenyltrifluoromethanesulfonamide was added. The ice bath was allowed to melt and the reaction mixture was stirred overnight at room temperature. Water was added and the aqueous layer was extracted with ethyl acetate (3 X 1 vol). The organic layer was washed with brine and then dried over magnesium sulfate, filtered and then concentrated. The crude product was purified by flash chromatography (hexane/ethyl acetate 8 : 1) to give the title compound (17.8 g) as a waxy solid. ¹HNMR (200 MHz, CDCl₃): 7.65-7.14 (m, 4 H), 6.66 (s, 1 H), 4.30-4.15 (m, 2 H), 3.24-2.96 (m, 2H), 2.06 (dt, 2 H), 1.50 (s, 9 H), 1.49-1.38 (m, 2 H).

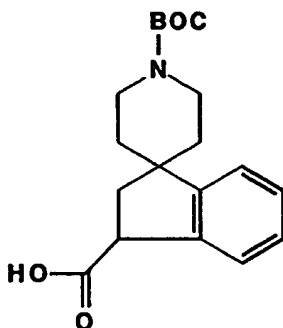
Step S:

- 82 -

A solution of 17.4 g of the intermediate from Step R, 11.0 ml of triethylamine, 634 mg of triphenylphosphine, and 240 mg of palladium acetate in 72 ml of ethanol and 158.0 ml of DMF was purged for 10 minutes with carbon monoxide and then stirred under a carbon monoxide atmosphere for 24 hours. The ethanol was removed in vacuum and the reaction mixture was diluted with water and extracted repeatedly with ethyl acetate. The ethyl acetate layer was washed with 1N HCl, water, and brine and then dried over magnesium sulfate, filtered and concentrated. Purification by flash chromatography (hexane/ethyl acetate 8:1) provided 27.6 g of the title compound as a colorless oil.

¹HNMR (200 MHz, CDCl₃): 8.0-7.94 (m, 1H), 7.7 (s, 1 H), 7.4-7.25 (m, 3H), 4.4 (q, 2H), 4.25-4.15 (m, 2H), 3.13 (dt, 2H), 2.03 (dt, 2H), 1.5 (s, 9H), 1.55-1.35 (m, 2H), 1.4 (t, 3H).

15 Step T:

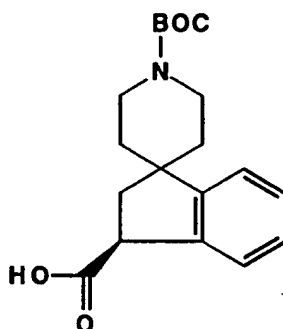


To a suspension of Pd/C (1.7g) in ethanol (300 ml) was added the title compound (27 g) from Step S. The reaction mixture was purged with hydrogen and then shaken under a hydrogen atmosphere for 3 hours. The mixture was purged with nitrogen and filtered through celite and concentrated to give the title compound (27 g). The crude product was dissolved in ethanol (200 ml) and 2N sodium hydroxide (76 ml) was added. The reaction mixture was heated to 50 °C for three hours then cooled and the ethanol was removed under vacuum and the residue was dissolved in ethyl acetate. 1N HCl was added and the layers were separated and the aqueous layer was extracted with ethyl acetate (3 x 1 vol). The combined organic layers were washed with saturated aqueous

- 83 -

NaCl, dried over anhydrous sodium sulfate, filtered and concentrated to provide the title compound (23.8 g) as a white solid. ^1H NMR (200 MHz, CDCl_3): 7.50-7.42 (m, 1 H), 7.34-7.12 (m, 3 H), 4.22-4.04 (m, 3 H), 3.06-2.84 (m, 2 H), 2.40 (d, 2 H), 1.88-1.6 (m, 4 H), 1.50 (s, 9 H).

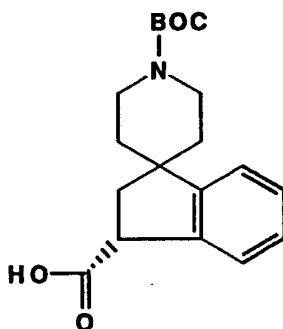
5

Step U:

The acid from Step T (23.5 g, 0.07 mol) was dissolved in
10 toluene (150 ml) and R- methylbenzylamine (9.02 ml) was added. The
toluene solution was heated on a steam bath until everything was in
solution. The solution was then seeded with crystals grown in the same
way on a much smaller scale. The solution was allowed to sit overnight
and then the mixture was filtered to give 15.8 g of crystals. The crystals
15 were recrystallized from toluene two more times. The crystals (12 g) were
dissolved in ethyl acetate /1 N HCl and the organic layer was washed
with 1 N HCL (2 X 1 vol) and brine. The organic layer was dried over
magnesium sulfate, filtered and concentrated to give 8.9 g of the title
compound. $[\alpha]_D^{20} = -16.9$ ($c = 0.84$, methanol)

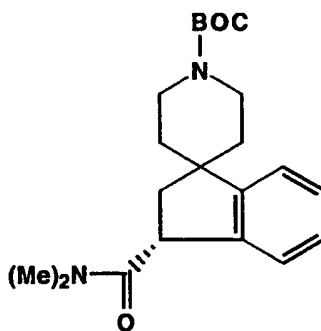
20

Step V:



The mother liqueurs from Step U were washed with 1 N HCl (2 x 1 vol) and brine dried over magnesium sulfate, filtered, and concentrated to give recovered acid (15.4 g). To this acid in toluene (100 mL) was added S-methylbenzylamine (5.95 mL). The crystals were recrystallized four times from toluene as above to give 12.3 g of salt. The salt was dissolved in ethyl acetate / 1 N HCl and washed with 1 N HCl (2 X 1 vol) and brine. The organic layer was dried over magnesium sulfate and filtered and concentrated to give the title compound (9.0 g). $[\alpha]_D^{25} = +17.1$ ($c = 1.06$, methanol).

Step W:



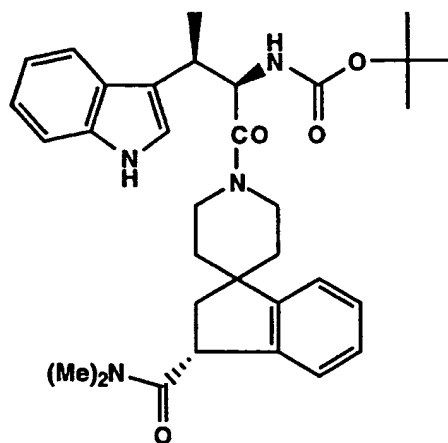
15 A solution of the title compound from Step V (14.0 g, 42 mMol) in dichloromethane was cooled to 0 °C and dimethylamine (25.4 mL, 2M in THF) was added. The mixture was stirred for ten minutes at 0 °C and then EDC and DMAP were added. The reaction mixture was stirred for four hours at 0 °C and then quenched with 1 N HCl. The

- 85 -

aqueous layers were extracted with dichloromethane and the combined organic layers were then washed with water and brine and dried over sodium sulfate. The crude product was purified by flash chromatography (dichloromethane/acetone 9:1) to give the title compound (12.2 g). HPLC analysis (chiralcel OD-R, 50% 0.5N NaClO₄ / 50% acetonitrile, 0.5 ml/min. E₁ retention time 20.8 min (E₁ prepared from the intermediate in Example 1 Step U as in Example 1 Step W; E₂ retention time 24.7 min) showed it to be approximately a 1 : 200 mixture of enantiomers.

¹HNMR (400 MHz, CDCl₃): 7.25-7.05(m, 4 H), 4.35 (t, 1 H), 4.20-4.10 (m, 2 H), 3.25 (s, 3 H), 3.05 (s, 3 H), 2.90-2.85 (m, 2H), 2.42-2.28 (m, 2H), 1.95 (dt, 1H), 1.75-1.60 (m, 2 H), 1.52-1.50 (m, 1 H), 1.49 (s, 9H).

Step X:

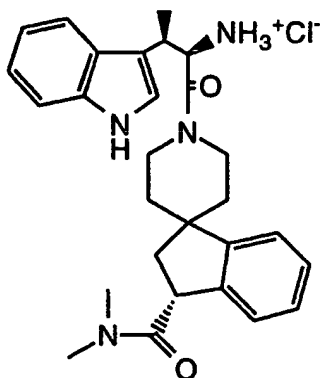


A sample of the title compound from Example 1 Step W was deprotected with a saturated solution of HCl in ethyl acetate as above to give the hydrochloride salt (6.3 g, 21 mmol). To this salt in dichloromethane at 0°C was added the intermediate prepared in Example 1 Step P (7.0 g, 22 mmol), HOBT (4.4g, 33 mmol), NMM (4.83 ml, 44 mmol) and finally EDC(6.3g, 33 mmol). The reaction mixture was warmed to room temperature and stirred overnight. It was then poured into ethyl acetate and washed with 1 N HCl, saturated bicarb, and brine then dried over magnesium sulfate. The organic layer was filtered and

- 86 -

concentrated. Purification by flash chromatography (ethyl acetate) provided the title compound (10 g, 17.9 mmol).

Step Y:

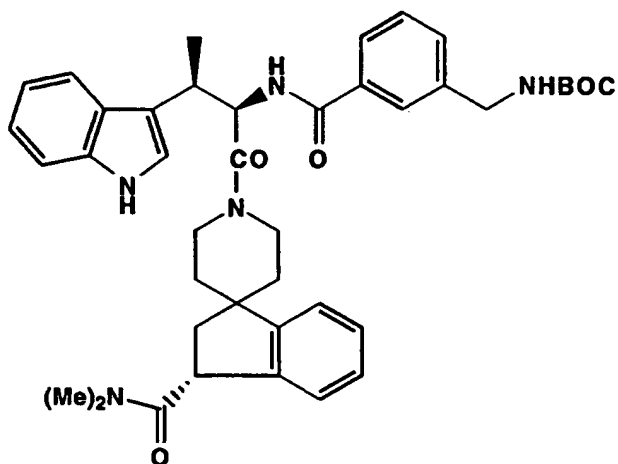


5

A solution of the N-Boc dipeptide from the previous step (1.32 g, 2.6 mmol) in ethyl acetate (8 mL) was cooled to 0°C. While stirring, HCl-EtOAc was added to the mixture (10 mL). The reaction was stirred for 20 minutes, until TLC analysis indicated that the reaction was complete. The solution was then concentrated to remove the ethyl acetate to afford 1.25g of the product (100%). ESI-MS calc. for C₂₈H₃₃N₄O₂: 457; Found 458 (M+H).

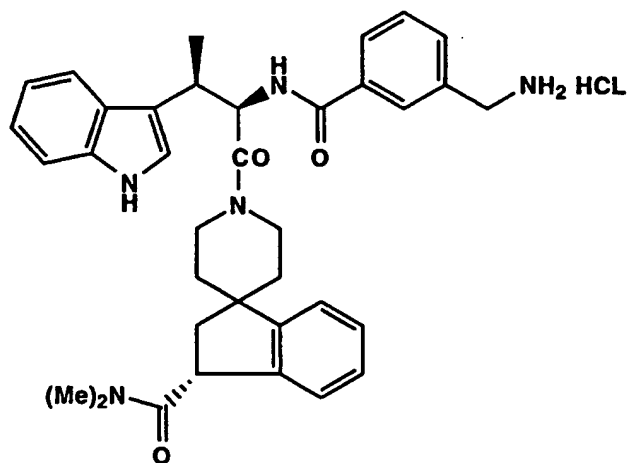
- 87 -

Step Z:



To a solution of the intermediate from the previous step in methylene chloride was added N-Boc-3-methylaminobenzoic acid (62 mg), EDC(58 mg), HOBT (41mg), and NMM (0.24ml). The reaction mixture was stirred overnight and then loaded onto a prepTLC plate. Elution with methylene chloride /acetone (8 :2) gave 79 mg .

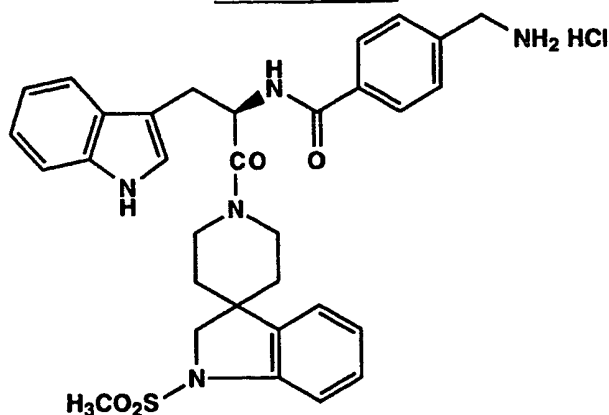
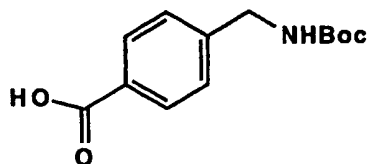
Step AA:



- 88 -

The intermediate from the previous step was stirred in ethyl acetate / HCl for two hours. Prep TLC purification gave 41 mg of the title compound. FAB-MS 592 (M+1).

5

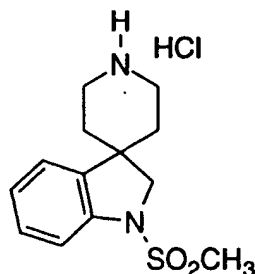
EXAMPLE 2Step A:

10

To a solution of 1.0g of 4-aminomethylbenzoic acid in 10mL of 1N NaOH, 10mL of water and 20mL of dioxane at 0°C was 1.7g of di-tert-butylcarbonate and stirred overnight. The reaction mixture was acidified to pH=2 and extracted with ethyl acetate. The combined organics were washed with brine, dried over anhydrous sodium sulfate and concentrated to give the desired compound as a white solid.

15

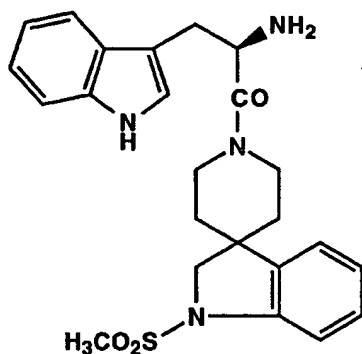
- 89 -

Step B:

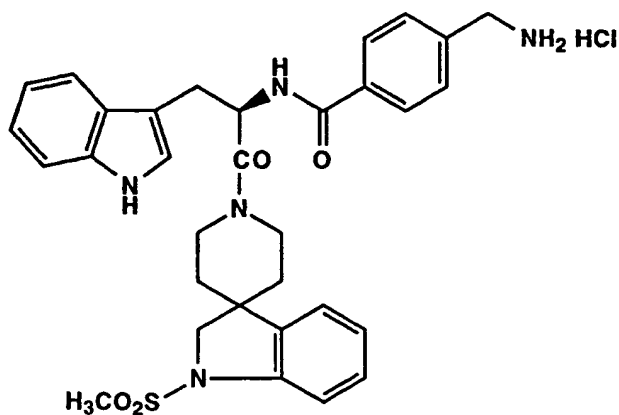
To a solution of 1.20 g (5.8mmol) of 1'-methyl-1,2-dihydro-spiro[3H-indole-3,4'-piperidine] (prepared as described in H. Ong *et al J. Med. Chem.* 1983, 23, 981-986) in 20 mL of dry dichloromethane at 0°C was added triethylamine (0.90 mL; 6.4 mmol) and methanesulfonyl chloride (0.49 mL; 6.35 mmol) and stirred for 30 min. The reaction mixture was poured into 15 mL of saturated aqueous sodium bicarbonate solution and extracted with dichloromethane (2X10 mL). The combined organics were washed with brine (20 mL), dried over anhydrous potassium carbonate, filtered and the solvent removed under reduced pressure to yield 1.44 g of the methanesulfonamide derivative as pale yellow oil which was used without purification.

To a solution of above crude product in 20 mL of dry 1,2-dichloroethane at 0°C was added 1.0 mL (9.30 mmol) of 1-chloroethyl chloroformate, and then stirred at RT for 30 min and finally at reflux for 1h. The reaction mixture was concentrated to approximately one third of the volume and then diluted with 20 mL of dry methanol and refluxed for 1.5h. The reaction was cooled to RT and concentrated to approximately one half of the volume. The precipitate was filtered and washed with a small volume of cold methanol. This yielded 1.0 g of the piperidine HCl salt as a white solid. The filtrate was concentrated and a small volume of methanol was added followed by ether. The precipitated material was once again filtered, washed with cold methanol, and dried. This gave an additional 0.49 g of the desired product. Total yield 1.49 g (70%). ¹H NMR(CDCl₃, 200MHz) δ 7.43-7.20 (m, 3H), 7.10 (dd, 1H), 3.98 (bs, 2H), 3.55-3.40 (bd, 2H), 3.35-3.10 (m, 2H), 2.99 (s, 3H), 2.15 (t, 2H), 2.00 (t, 2H).

- 90 -

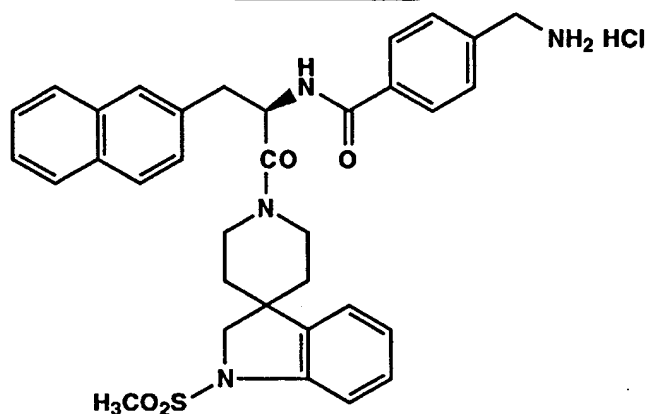
Step C:

- 5 To a suspension of 1.2 g of the piperidine prepared in Step B in 15 mL of acetonitrile was added 0.50 mL of N-methylmorpholine, 1.00 g of (2R, 3R)-N-tBOC-tryptophan, 0.80 g of HOBT, and 1.00 g of EDC and stirred at RT for 3h. The reaction mixture was diluted with 100 mL of ether and washed with 50 mL of 0.05N HCl, 50 mL of saturated sodium bicarbonate solution, dried over MgSO₄, and concentrated. A solution of the above intermediate in 50 mL of ethyl acetate at 0°C was treated with HCl (g) for 2 min. and then stirred for 1h. Dry ether (50 mL) was added, and the precipitated solid was collected by filtration.

15 Step D:

- 91 -

To a solution of 200mg of the amino intermediate from Step C in 5mL of chloroform was added 100mg of the acid intermediate from Step A, 65mg of EDC and 110mg of HOBT and stirred at room temperature for 16h. The reaction mixture was diluted with 20mL of dichloromethane, washed with 0.5N HCl (2X10mL), saturated sodium bicarbonate solution, dried over anhydrous sodium sulfate and concentrated. This material was purified by flash chromatography with hexane-ethyl acetate (2:1) as the eluent to give the desired product. This material was dissolved in 3mL of ethyl acetate was treated with HCl (gas) for 1 min. and stirred for 30 minutes. Ether was added and the precipitate was collected by filtration. FABMS Calcd. for C₃₂H₃₃N₅O₄S 585; Found 586.1 (m+1).

EXAMPLE 3

15

The title compound was prepared from N-tBoc-2-naphthyl alanine and the protected acid synthesized in Step A of Example 2 as described in the experimental for Example 2. FABMS Calcd. for C₃₄H₃₆N₄O₄S 596; Found 597.2 (m+1).

20

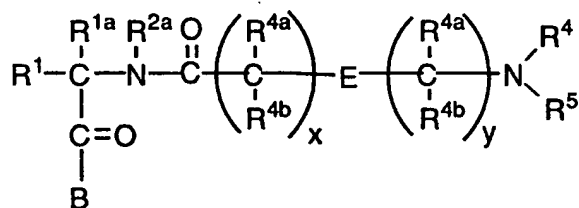
- 92 -

While the invention has been described and illustrated with reference to certain particular embodiments thereof, those skilled in the art will appreciate that various adaptations, changes, modifications, substitutions, deletions, or additions of procedures and protocols may be made without departing from the spirit and scope of the invention. For example, effective dosages other than the particular dosages as set forth herein above may be applicable as a consequence of variations in the responsiveness of the mammal being treated for any of the indications with the compounds of the invention indicated above. Likewise, the specific pharmacological responses observed may vary according to and depending upon the particular active compounds selected or whether there are present pharmaceutical carriers, as well as the type of formulation and mode of administration employed, and such expected variations or differences in the results are contemplated in accordance with the objects and practices of the present invention. It is intended, therefore, that the invention be defined by the scope of the claims which follow and that such claims be interpreted as broadly as is reasonable.

- 93 -

WHAT IS CLAIMED IS:

1. A compound of the formula:



Formula I

wherein:

R^1 is selected from the group consisting of:

- 10 C_1 - C_{10} alkyl, -aryl-, aryl (C_1 - C_6 alkyl)-, heteroaryl-, heteroaryl(C_1 - C_6 alkyl)-, (C_3 - C_7 cycloalkyl)-(C_1 - C_6 alkyl)-, (C_1 - C_5 alkyl)-K-(C_1 - C_5 alkyl)-, aryl-(C_0 - C_5 alkyl)-K-(C_1 - C_5 alkyl)-, 15 heteroaryl-(C_0 - C_5 alkyl)-K-(C_1 - C_5 alkyl)-, and (C_3 - C_7 cycloalkyl)-(C_0 - C_5 alkyl)-K-(C_1 - C_5 alkyl)-, wherein K is -O-, -S(O)_m-, -N(R²)C(O)-, -C(O)N(R²)-, -OC(O)-, -C(O)O-, -CR²=CR²- or -C≡C-, wherein R² and the alkyl groups may be further substituted with 1 to 9 20 halo, -S(O)_mR^{2a}, 1 to 3 of -OR^{2a}, or -C(O)OR^{2a}, and wherein aryl is phenyl or naphthyl, and heteroaryl is selected from indolyl, thiophenyl, benzofuranyl, benzothiophenyl, aza-indolyl, pyridinyl, quinolinyl, and benzimidazolyl, wherein aryl and heteroaryl are unsubstituted or substituted with phenyl, phenoxy, halophenyl, 1 to 3 of -C₁-C₆ alkyl, 1 to 25 3 of halo, 1 to 2 of -OR², methylenedioxy, -S(O)_mR², 1 to 2 of -CF₃, -OCF₃, nitro, -N(R²)(R²), -N(R²)C(O)(R²), -C(O)OR², -C(O)N(R²)(R²), -SO₂N(R²)(R²), -N(R²)SO₂-aryl, or -N(R²)SO₂R²;

R^{1a} is hydrogen or C₁-C₄ alkyl;

30

- 94 -

R^2 is selected from the group consisting of:

hydrogen, -C₁-C₆ alkyl, -C₃-C₇ cycloalkyl, and -CH₂-phenyl,

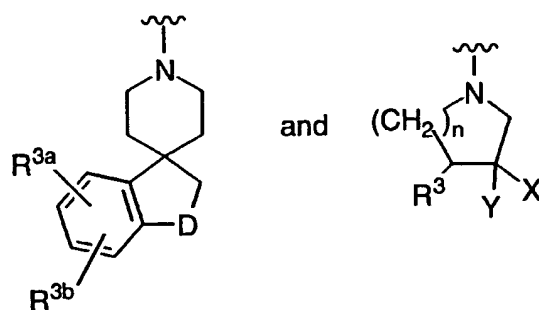
wherein the alkyl or the cycloalkyl is unsubstituted or substituted with

hydroxyl, C₁-C₃ alkoxy, thioalkyl, C(O)OR^{2a}, and where, if two -C₁-C₆

- 5 alkyl groups are present on one atom, they may be joined to form a C₃-C₈ cyclic ring being selected from the group consisting of pyrrolidine, piperidine, piperazine, morpholine, thiomorpholine, optionally substituted by hydroxyl;

- 10 R^{2a} is hydrogen or C₁-C₆ alkyl;

B is selected from:



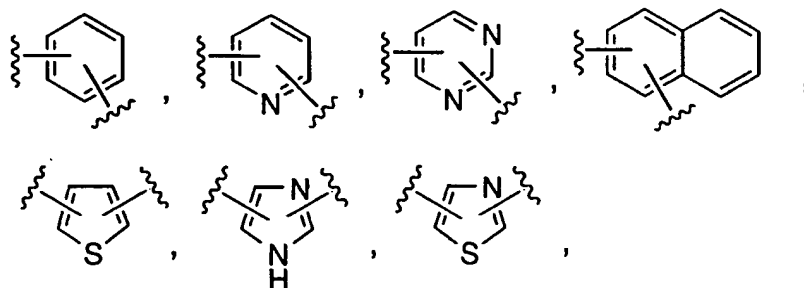
- R^3 is selected from: hydrogen, -(CH₂)_rphenyl, -(CH₂)_rpyridyl, -
- 15 (CH₂)_rthienyl, -(CH₂)_rbenzimidazolyl, -(CH₂)_rquinoliny, - (CH₂)_rnaphthyl, -(CH₂)_rindolyl, -C₁-C₁₀ alkyl, -C₃-C₇ cycloalkyl, where the phenyl, pyridyl, naphthyl, indolyl, thienyl, benzimidazolyl, quinoliny, and C₃-C₇ cycloalkyl rings may be substituted by 1 to 3 substituents selected from the group consisting of: C₁-C₆ alkyl, halogen,
- 20 -OR², -NHSO₂CF₃, -(CH₂)_rOR⁶, -(CH₂)_rN(R²)(R⁶), -(CH₂)_r(R⁶), - (CH₂)_rC(O)OR², -(CH₂)_rC(O)OR⁶, -(CH₂)_rOC(O)R², - (CH₂)_rOC(O)R⁶, -(CH₂)_rC(O)R², -(CH₂)_rC(O)R⁶, - (CH₂)_rC(O)N(R²)(R²), -(CH₂)_rC(O)N(R²)(R⁶), - (CH₂)_rN(R²)C(O)(R²), -(CH₂)_rN(R²)C(O)R⁶ -(CH₂)_rN(R⁶)C(O)R², -
- 25 (CH₂)_rN(R⁶)C(O)R⁶, -(CH₂)_rN(R²)C(O)OR², -(CH₂)_rN(R²)C(O)OR⁶, -(CH₂)_rN(R⁶)C(O)OR², -(CH₂)_rN(R⁶)C(O)OR⁶, -

- 95 -

- $(\text{CH}_2)_r\text{N}(\text{R}^2)\text{C}(\text{O})\text{N}(\text{R}^2)(\text{R}^6)$, $-(\text{CH}_2)_r\text{N}(\text{R}^2)\text{C}(\text{O})\text{N}(\text{R}^2)(\text{R}^2)$, -
 $(\text{CH}_2)_r\text{N}(\text{R}^6)\text{C}(\text{O})\text{N}(\text{R}^2)(\text{R}^6)$, $-(\text{CH}_2)_r\text{N}(\text{R}^2)\text{SO}_2\text{R}^2$, -
 $(\text{CH}_2)_r\text{N}(\text{R}^6)\text{SO}_2\text{R}^2$, $-(\text{CH}_2)_r\text{N}(\text{R}^6)\text{SO}_2\text{R}^6$, $-(\text{CH}_2)_r\text{OC}(\text{O})\text{N}(\text{R}^2)(\text{R}^6)$, -
 $(\text{CH}_2)_r\text{OC}(\text{O})\text{N}(\text{R}^2)(\text{R}^2)$, $-(\text{CH}_2)_r\text{SO}_2\text{N}(\text{R}^2)(\text{R}^6)$, -
 5 $(\text{CH}_2)_r\text{OC}(\text{O})\text{N}(\text{R}^2)(\text{R}^2)$, $-(\text{CH}_2)_r\text{SO}_2\text{N}(\text{R}^2)(\text{R}^6)$, -
 $(\text{CH}_2)_r\text{SO}_2\text{N}(\text{R}^2)(\text{R}^2)$, $-(\text{CH}_2)_r\text{N}(\text{R}^2)\text{SO}_2\text{N}(\text{R}^2)(\text{R}^6)$, -
 $(\text{CH}_2)_r\text{N}(\text{R}^6)\text{SO}_2\text{N}(\text{R}^2)(\text{R}^6)$, $-(\text{CH}_2)_r\text{S}(\text{O})_m\text{R}^6$, and $-(\text{CH}_2)_r\text{S}(\text{O})_m\text{R}^2$;

- R^{3a} and R^{3b} are independently selected from: hydrogen, phenyl,
 10 phenoxy, halophenyl, $-\text{C}_1-\text{C}_6$ alkyl, halogen, $-\text{OR}^2$, methylenedioxy, -
 $\text{S}(\text{O})_m\text{R}^2$, $-\text{CF}_3$, $-\text{OCF}_3$, nitro, $-\text{N}(\text{R}^2)(\text{R}^2)$, $-\text{N}(\text{R}^2)\text{C}(\text{O})(\text{R}^2)$, $-\text{C}(\text{O})\text{OR}^2$,
 $-\text{C}(\text{O})\text{N}(\text{R}^2)(\text{R}^2)$, $-\text{SO}_2\text{N}(\text{R}^2)(\text{R}^2)$, $-\text{N}(\text{R}^2)\text{SO}_2$ -aryl, and $-\text{N}(\text{R}^2)\text{SO}_2\text{R}^2$;

E is selected from: $-\text{O}-$, $-\text{S}-$, $-\text{CH}=\text{CH}-$,



15

which is optionally substituted with a substituent selected from: halo, hydroxy, $-\text{N}(\text{R}^2)(\text{R}^2)$, C_1-C_6 alkyl and C_1-C_6 alkoxy;

- R^4 and R^5 are independently selected from hydrogen, C_1-C_6 alkyl, and
 20 substituted C_1-C_6 alkyl where the substituents are selected from halo,
 hydroxy, phenyl, and C_1-C_6 alkoxy; carbonyl;
 or R^5 and R^4 may be taken together to form $-(\text{CH}_2)_d-\text{L}_a(\text{CH}_2)_e-$ where
 L_a is $-\text{C}(\text{R}^2)_2-$, $-\text{O}-$, $-\text{S}(\text{O})_m-$ or $-\text{N}(\text{R}^2)-$, d and e are independently 1 to 3
 and R^2 is as defined above;

25

- 96 -

R^{4a} and R^{4b} are independently selected from: hydrogen, C₁-C₆ alkyl, trifluoromethyl, phenyl, or substituted C₁-C₆ alkyl where the substituents are selected from: imidazolyl, naphthyl, phenyl, indolyl, p-hydroxyphenyl, -OR², -S(O)_mR², -C(O)OR², C₃-C₇ cycloalkyl, -
 5 N(R²)(R²), -C(O)N(R²)(R²); or R^{4a} and R^{4b} may independently be joined to one or both of R⁴ or E (where E is other than -O-, -S-, or -CH=CH-) to form an alkylene bridge between the terminal nitrogen and the alkyl portion of the R^{4a} or R^{4b} and the R⁴ E group, wherein the bridge contain 1 to 8 carbons atoms; or R^{4a} and R^{4b} may be joined to
 10 one another to form C₃-C₇ cycloalkyl;

R⁶ is selected from: hydrogen, C₁-C₆ alkyl, and (CH₂)_varyl, wherein the (CH₂)_v and alkyl groups may be optionally substituted by -O(R²), -S(O)_mR², -C(O)OR², -C(O)N(R²)(R²), -SO₂N(R²)(R²), or -
 15 N(R²)C(O)N(R²)(R²), wherein the aryl group is selected from: phenyl, pyridyl, 1H-tetrazolyl, triazolyl, oxadiazolyl, pyrazolyl, thiadiazoyl, and benzimidazol-2-yl, which is optionally substituted with C₁-C₆ alkyl, C₃-C₆ cycloalkyl, amino, or hydroxyl;

20 X is selected from the group consisting of: hydrogen, -C≡N, - (CH₂)_qN(R²)C(O)R², -(CH₂)_qN(R²)C(O)(CH₂)_taryl, - (CH₂)_qN(R²)SO₂(CH₂)_taryl, -(CH₂)_qN(R²)SO₂R², - (CH₂)_qN(R²)C(O)N(R²)(CH₂)_taryl, -(CH₂)_qN(R²)C(O)N(R²)(R²), - (CH₂)_qC(O)N(R²)(R²), -(CH₂)_qC(O)N(R²)(CH₂)_taryl, -
 25 (CH₂)_qC(O)OR², -(CH₂)_qC(O)O(CH₂)_taryl, -(CH₂)_qOR², - (CH₂)_qOC(O)R², -(CH₂)_qOC(O)(CH₂)_taryl, -(CH₂)_qOC(O)N(R²)(R²), -(CH₂)_qC(O)R², -(CH₂)_qC(O)(CH₂)_taryl, -(CH₂)_qN(R²)C(O)OR², - (CH₂)_qN(R²)SO₂N(R²)(R²), -(CH₂)_qS(O)_mR², and - (CH₂)_qS(O)_m(CH₂)_taryl, where R², (CH₂)_q and (CH₂)_t group may be
 30 optionally substituted with C₁-C₄ alkyl, hydroxyl, C₁-C₄ lower alkoxy, carboxyl, N(R²)(R²), CONH₂, S(O)_mCH₃, carboxylate C₁-C₄ alkyl esters, or 1H-tetrazol-5-yl, and aryl is phenyl, naphthyl, pyridyl, thiazolyl, or 1H-tetrazol-5-yl groups which may be optionally substituted with

- 97 -

halogen, $-OR^2$, $-CON(R^2)(R^2)$, $-C(O)OR^2$, C1-C4 alkyl, $-S(O)_mR^2$, or 1H-tetrazol-5-yl;

Y is selected from the group consisting of:

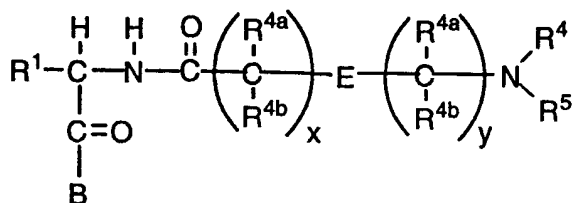
- 5 hydrogen, C1-C10 alkyl, $-(CH_2)_t$ aryl, $-(CH_2)_q$ (C3-C7 cycloalkyl), $-(CH_2)_q$ -K-(C1-C6 alkyl), $-(CH_2)_q$ -K- $(CH_2)_t$ aryl, $-(CH_2)_q$ -K- $(CH_2)_t$ (C3-C7 cycloalkyl containing O, NR^2 S) and $-(CH_2)_q$ -K- $(CH_2)_t$ (C3-C7 cycloalkyl), where K is $-O-$, $-S(O)_m-$, $-C(O)NR^2-$, $-CH=CH-$, $-C\equiv C-$, $-N(R^2)C(O)-$, $-C(O)NR^2-$, $-C(O)O-$, or $-OC(O)-$, and where the alkyl, R^2 , $(CH_2)_q$ and $(CH_2)_t$ groups are optionally substituted by C1-C4 alkyl, hydroxyl, C1-C4 lower alkoxy, carboxyl, $-CONH_2$ or a carboxylate C1-C4 alkyl ester, and aryl is phenyl, naphthyl, pyridyl, 1-H-tetrazol-5-yl, thiazolyl, imidazolyl, indolyl, oxadiazolyl, pyrimidinyl, thiadiazolyl, pyrazolyl, oxazolyl, isoxazolyl,
- 15 thiophenyl, quinolinyl, pyrazinyl, or isothiazolyl which is optionally substituted with halogen, $-OR^2$, $-C(O)OR^2$, $N(R^2)(R^2)$, $-C(O)N(R^2)(R^2)$, nitro, cyano, benzyl, C1-C4 alkyl, $-S(O)_mR^2$, or 1H-tetrazol-5-yl;
- 20 D is selected from: $-N(R^7)-$, $-S(O)_m-$, $-C(O)-$ and $-C(H)(R^7)-$, wherein R^7 is selected from: $-R^2$, $-OR^2$, $-(CH_2)_q$ aryl, $-C(O)R^2$, $-C(O)(CH_2)_q$ aryl, $-SO_2R^2$, $-SO_2(CH_2)_q$ aryl, $-C(O)N(R^2)(R^2)$, $-C(O)N(R^2)(CH_2)_q$ aryl, $-C(O)OR^2$, 1-H-tetrazol-5-yl, $-SO_2N(R^2)$ aryl, $-SO_2N(R^2)(R^2)$ and the $(CH_2)_q$ may be optionally substituted by C1-C4
- 25 alkyl, and the R^2 and aryl may be optionally further substituted with a substituent selected from: $-OR^{2a}$, $-O(CH_2)_q$ aryl, $-C(O)OR^{2a}$, $-C(O)(CH_2)_q$ aryl, $-C(O)N(R^{2a})(R^{2a})$, $-C(O)N(R^{2a})(CH_2)_1$ aryl, halogen, $-N(R^{2a})(R^{2a})$, C1-C4 alkyl, 1,2,4-triazolyl, 1-H-tetrazol-5-yl, $-C(O)NHSO_2R^{2a}$, $-S(O)_mR^{2a}$, $-C(O)NHSO_2(CH_2)_q$ aryl, $-N(R^2)C(O)N(R^{2a})(R^{2a})$, $-N(R^{2a})C(O)N(R^{2a})(CH_2)_q$ aryl, $-N(R^{2a})(R^{2a})$, $-N(R^{2a})C(O)R^{2a}$, $-N(R^{2a})C(O)(CH_2)_q$ aryl, $-OC(O)N(R^{2a})(R^{2a})$, $-OC(O)N(R^{2a})(CH_2)_q$ aryl;
- 30

- 98 -

- 1 is 0, 1 or 2;
 m is 0, 1, or 2;
 n is 0, 1, or 2;
 q is 0, 1, 2, 3, or 4;
 5 r is 0, 1, 2, or 3;
 t is 0, 1, 2, or 3;
 v is 0, 1, or 2;
 x is 0, 1, 2, or 3;
 y is 0, 1, 2, or 3, with the proviso that if E is -O- or -S-, y is other than 0
 10 or 1, and with the further proviso that if E is -CH=CH-, y is other than 0;

and pharmaceutically acceptable salts and individual diastereomers thereof.

- 15 2. The compound of Claim 1 of the formula:



Formula Ia

wherein:

- 20 R^1 is selected from the group consisting of:
 C₁-C₁₀ alkyl, -aryl-, aryl (C₁-C₆ alkyl)-,
 heteroaryl-, heteroaryl(C₁-C₆ alkyl)-,
 (C₃-C₇ cycloalkyl)-(C₁-C₆ alkyl)-,
 (C₁-C₅ alkyl)-K-(C₁-C₅ alkyl)-,
 25 aryl-(C₀-C₅ alkyl)-K-(C₁-C₅ alkyl)-,
 heteroaryl-(C₀-C₅ alkyl)-K-(C₁-C₅ alkyl)-, and
 (C₃-C₇ cycloalkyl)-(C₀-C₅ alkyl)-K-(C₁-C₅ alkyl)-,
 wherein K is -O-, -S(O)_m-, -N(R²)C(O)-, -C(O)N(R²)-, -OC(O)-,
 -C(O)O-, -CR²=CR²- or -C≡C-,

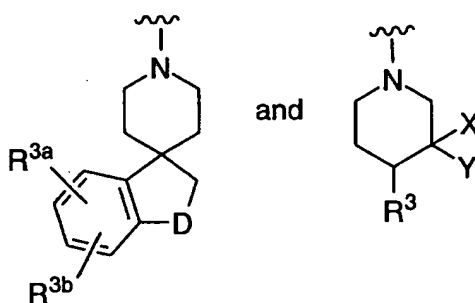
- 99 -

wherein R^2 and the alkyl groups may be further substituted with 1 to 9 halo, $-S(O)_mR^{2a}$, 1 to 3 of $-OR^{2a}$, or $-C(O)OR^{2a}$, and wherein aryl is phenyl or naphthyl, and heteroaryl is selected from indolyl, thiophenyl, benzofuranyl, benzothiophenyl, aza-indolyl, pyridinyl, quinolinyl, and benzimidazolyl, wherein aryl and heteroaryl are unsubstituted or substituted with phenyl, phenoxy, halophenyl, 1 to 3 of $-C_1-C_6$ alkyl, 1 to 3 of halo, 1 to 2 of $-OR^2$, methylenedioxy, $-S(O)_mR^2$, 1 to 2 of $-CF_3$, $-OCF_3$, nitro, $-N(R^2)(R^2)$, $-N(R^2)C(O)(R^2)$, $-C(O)OR^2$, $-C(O)N(R^2)(R^2)$, $-SO_2N(R^2)(R^2)$, $-N(R^2)SO_2$ -aryl, or $-N(R^2)SO_2R^2$;

10

R^2 is selected from the group consisting of: hydrogen, $-C_1-C_6$ alkyl, $-C_3-C_7$ cycloalkyl, and $-CH_2$ -phenyl, wherein the alkyl or the cycloalkyl is unsubstituted or substituted with hydroxyl, C_1-C_3 alkoxy, thioalkyl, $-C(O)OR^{2a}$, and wherein, if two $-C_1-C_6$ alkyl groups are present on one atom, the groups may be optionally joined to form a C_3-C_8 cyclic ring being selected from the group consisting of pyrrolidine, piperidine, piperazine, morpholine, thiomorpholine;

20 B is selected from:



R^3 is selected from: hydrogen, phenyl, pyridyl, naphthyl, indolyl, benzimidazolyl, thienyl, quinolinyl, where the phenyl, pyridyl, naphthyl, benzimidazolyl, thienyl, quinolinyl, and indolyl may be substituted by 1 to 3 substituents selected from the group consisting of: C_1-C_6 alkyl, halogen, $-OR^2$, $-(CH_2)_rOR^6$, $-(CH_2)_rN(R^2)(R^6)$, $-(CH_2)_r(R^6)$, -

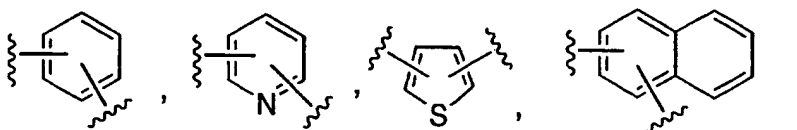
25

- 100 -

$(\text{CH}_2)_r\text{C}(\text{O})\text{OR}^2$, $-(\text{CH}_2)_r\text{C}(\text{O})\text{OR}^6$, $-(\text{CH}_2)_r\text{C}(\text{O})\text{R}^2$, $-(\text{CH}_2)_r\text{C}(\text{O})\text{R}^6$, -
 $(\text{CH}_2)_r\text{C}(\text{O})\text{N}(\text{R}^2)(\text{R}^2)$, $-(\text{CH}_2)_r\text{C}(\text{O})\text{N}(\text{R}^2)(\text{R}^6)$, -
 $(\text{CH}_2)_r\text{N}(\text{R}^2)\text{C}(\text{O})(\text{R}^2)$, $-(\text{CH}_2)_r\text{N}(\text{R}^2)\text{C}(\text{O})\text{R}^6$, $-(\text{CH}_2)_r\text{N}(\text{R}^6)\text{C}(\text{O})\text{R}^2$, -
 $(\text{CH}_2)_r\text{N}(\text{R}^6)\text{C}(\text{O})\text{R}^6$, $-(\text{CH}_2)_r\text{N}(\text{R}^2)\text{C}(\text{O})\text{OR}^2$, $-(\text{CH}_2)_r\text{N}(\text{R}^2)\text{C}(\text{O})\text{OR}^6$,
 5 $-(\text{CH}_2)_r\text{N}(\text{R}^6)\text{C}(\text{O})\text{OR}^2$, $-(\text{CH}_2)_r\text{N}(\text{R}^6)\text{C}(\text{O})\text{OR}^6$, -
 $(\text{CH}_2)_r\text{N}(\text{R}^2)\text{C}(\text{O})\text{N}(\text{R}^2)(\text{R}^6)$, $-(\text{CH}_2)_r\text{N}(\text{R}^2)\text{C}(\text{O})\text{N}(\text{R}^2)(\text{R}^2)$, -
 $(\text{CH}_2)_r\text{N}(\text{R}^6)\text{C}(\text{O})\text{N}(\text{R}^2)(\text{R}^6)$, $-(\text{CH}_2)_r\text{N}(\text{R}^2)\text{SO}_2\text{R}^2$, -
 $(\text{CH}_2)_r\text{N}(\text{R}^6)\text{SO}_2\text{R}^2$, $-(\text{CH}_2)_r\text{N}(\text{R}^6)\text{SO}_2\text{R}^6$, $-(\text{CH}_2)_r\text{OC}(\text{O})\text{N}(\text{R}^2)(\text{R}^6)$, -
 $(\text{CH}_2)_r\text{SO}_2\text{N}(\text{R}^2)(\text{R}^6)$, $-(\text{CH}_2)_r\text{SO}_2\text{N}(\text{R}^2)(\text{R}^6)$, $-(\text{CH}_2)_r\text{SO}_2\text{N}(\text{R}^2)(\text{R}^2)$,
 10 $-(\text{CH}_2)_r\text{S}(\text{O})_m\text{R}^6$, and $-(\text{CH}_2)_r\text{S}(\text{O})_m\text{R}^2$;

R^{3a} and R^{3b} are independently selected from: hydrogen, phenyl,
 phenoxy, halophenyl, $\text{C}_1\text{-C}_6$ alkyl, halogen, $-\text{OR}^2$, methylenedioxy, -
 $\text{S}(\text{O})_m\text{R}^2$, $-\text{CF}_3$, $-\text{OCF}_3$, nitro, $-\text{N}(\text{R}^2)(\text{R}^2)$, $-\text{N}(\text{R}^2)\text{C}(\text{O})(\text{R}^2)$, $-\text{C}(\text{O})\text{OR}^2$,
 15 $-\text{C}(\text{O})\text{N}(\text{R}^2)(\text{R}^2)$, $-\text{SO}_2\text{N}(\text{R}^2)(\text{R}^2)$, $-\text{N}(\text{R}^2)\text{SO}_2\text{-aryl}$, and $-\text{N}(\text{R}^2)\text{SO}_2\text{R}^2$;

E is selected from: $-\text{O}-$, $-\text{S}-$, $-\text{CH}=\text{CH}-$,



which is optionally substituted with a substituent selected
 20 from: halo, hydroxy, $-\text{N}(\text{R}^2)(\text{R}^2)$, $\text{C}_1\text{-C}_6$ alkyl and $\text{C}_1\text{-C}_6$ alkoxy;

R^4 and R^5 are independently selected from hydrogen, $\text{C}_1\text{-C}_6$ alkyl, and
 substituted $\text{C}_1\text{-C}_6$ alkyl where the substituents are selected from halo,
 hydroxy, phenyl, and $\text{C}_1\text{-C}_6$ alkoxy; carbonyl;
 25 or R^5 and R^4 may be taken together to form $-(\text{CH}_2)_d\text{-L}_a(\text{CH}_2)_e-$ where
 L_a is $-\text{C}(\text{R}^2)_2-$, $-\text{O}-$, $-\text{S}(\text{O})_m-$ or $-\text{N}(\text{R}^2)-$, d and e are independently 1 to 3
 and R^2 is as defined above;

- 101 -

- R^{4a} and R^{4b} are independently selected from: hydrogen, C₁-C₆ alkyl, trifluoromethyl, phenyl, or substituted C₁-C₆ alkyl where the substituents are selected from: imidazolyl, naphthyl, phenyl, indolyl, p-hydroxyphenyl, -OR², -S(O)_mR², -C(O)OR², C₃-C₇ cycloalkyl, -
- 5 N(R²)(R²), -C(O)N(R²)(R²); or R^{4a} and R^{4b} may independently be joined to one or both of R⁴ or E (where E is other than -O-, -S-, or -CH=CH-) to form an alkylene bridge between the terminal nitrogen and the alkyl portion of the R^{4a} or R^{4b} and the R⁴ E group, wherein the bridge contain 1 to 5 carbons atoms; or R^{4a} and R^{4b} may be joined to
- 10 one another to form C₃-C₇ cycloalkyl;
- R⁶ is selected from: hydrogen, C₁-C₆ alkyl, and (CH₂)_varyl, wherein the (CH₂)_v and alkyl groups may be optionally substituted by -O(R²), -S(O)_mR², -C(O)OR², -C(O)N(R²)(R²), -SO₂N(R²)(R²), or -
- 15 N(R²)C(O)N(R²)(R²), wherein the aryl group is selected from: phenyl, pyridyl, 1H-tetrazolyl, triazolyl, oxadiazolyl, pyrazolyl, thiadiazoyl, and benzimidazol-2-yl, which is optionally substituted with C₁-C₆ alkyl, C₃-C₆ cycloalkyl, amino, or hydroxyl;
- 20 X is selected from the group consisting of: hydrogen, -C≡N, - (CH₂)_qN(R²)C(O)R², -(CH₂)_qN(R²)C(O)(CH₂)_taryl, - (CH₂)_qN(R²)SO₂(CH₂)_taryl, -(CH₂)_qN(R²)SO₂R², - (CH₂)_qN(R²)C(O)N(R²)(CH₂)_taryl, -(CH₂)_qN(R²)C(O)N(R²)(R²), - (CH₂)_qC(O)N(R²)(R²), -(CH₂)_qC(O)N(R²)(CH₂)_taryl, -
- 25 (CH₂)_qC(O)OR², -(CH₂)_qC(O)O(CH₂)_taryl, -(CH₂)_qOR², - (CH₂)_qOC(O)R², -(CH₂)_qOC(O)(CH₂)_taryl, -(CH₂)_qOC(O)N(R²)(R²), -(CH₂)_qC(O)R², -(CH₂)_qC(O)(CH₂)_taryl, -(CH₂)_qN(R²)C(O)OR², - (CH₂)_qN(R²)SO₂N(R²)(R²), -(CH₂)_qS(O)_mR², and - (CH₂)_qS(O)_m(CH₂)_taryl, where R², (CH₂)_q and (CH₂)_t group may be
- 30 optionally substituted with C₁-C₄ alkyl, hydroxyl, C₁-C₄ lower alkoxy, carboxyl, N(R²)(R²), CONH₂, S(O)_mCH₃, carboxylate C₁-C₄ alkyl esters, or 1H-tetrazol-5-yl, and aryl is phenyl, naphthyl, pyridyl, thiazolyl, or 1H-tetrazol-5-yl groups which may be optionally substituted with

- 102 -

halogen, $-OR^2$, $-CON(R^2)(R^2)$, $-C(O)OR^2$, C₁-C₄ alkyl, $-S(O)_mR^2$, or 1H-tetrazol-5-yl;

Y is selected from the group consisting of:

- 5 hydrogen, C₁-C₁₀ alkyl, $-(CH_2)_t$ aryl, $-(CH_2)_q$ (C₃-C₇ cycloalkyl), $-(CH_2)_q$ -K-(C₁-C₆ alkyl), $-(CH_2)_q$ -K-(CH₂)_taryl, $-(CH_2)_q$ -K-(CH₂)_t(C₃-C₇ cycloalkyl containing O, NR² S) and $-(CH_2)_q$ -K-(CH₂)_t(C₃-C₇ cycloalkyl), where K is O, S(O)_m, C(O)NR², CH=CH, C≡C, N(R²)C(O), C(O)NR², C(O)O, or OC(O), and
- 10 where the alkyl, R², (CH₂)_q and (CH₂)_t groups are optionally substituted by C₁-C₄ alkyl, hydroxyl, C₁-C₄ lower alkoxy, carboxyl, $-CONH_2$ or a carboxylate C₁-C₄ alkyl ester, and aryl is phenyl, naphthyl, pyridyl, 1-H-tetrazol-5-yl, thiazolyl, imidazolyl, indolyl, oxadiazolyl, pyrimidinyl, thiadiazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiophenyl, quinolinyl,
- 15 pyrazinyl, or isothiazolyl which is optionally substituted with halogen, $-OR^2$, $-C(O)OR^2$, N(R²)(R²), $-C(O)N(R^2)(R^2)$, nitro, cyano, benzyl, C₁-C₄ alkyl, $-S(O)_mR^2$, or 1H-tetrazol-5-yl;

- D is selected from: $-N(R^7)-$, $-S(O)_m-$, $-C(O)-$ and $-C(H)(R^7)-$,
- 20 wherein R⁷ is selected from: $-R^2$, $-(CH_2)_q$ aryl, $-C(O)R^2$, $-SO_2R^2$, $-C(O)N(R^2)(R^2)$, $-C(O)OR^2$, 1-H-tetrazol-5-yl, $-SO_2N(R^2)$ aryl, $-SO_2N(R^2)(R^2)$ and the (CH₂)_q may be optionally substituted by C₁-C₄ alkyl, and the R² and aryl may be optionally further substituted with a substituent selected from: $-OR^{2a}$, $-C(O)OR^{2a}$, $-C(O)N(R^{2a})(R^{2a})$,
- 25 halogen, C₁-C₄ alkyl, and the aryl is selected from of triazolyl, oxadiazolyl, thiadiazolyl, thiazolyl, imidazolyl, and 1H-tetrazolyl;

l is 0, 1 or 2;

m is 0, 1, or 2;

- 30 q is 0, 1, 2, 3, or 4;

r is 0, 1, 2, or 3;

t is 0, 1, 2, or 3;

v is 0, 1, or 2;

- 103 -

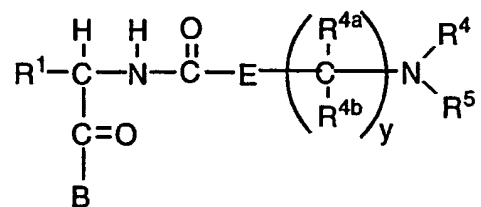
x is 0, 1, 2, or 3;

y is 0, 1, 2, or 3, with the proviso that if E is -O- or -S-, y is other than 0 or 1, and with the further proviso that if E is -CH=CH-, y is other than 0;

- 5 and pharmaceutically acceptable salts and individual diastereomers thereof.

- 104 -

3. The compound of Claim 1 of the formula:

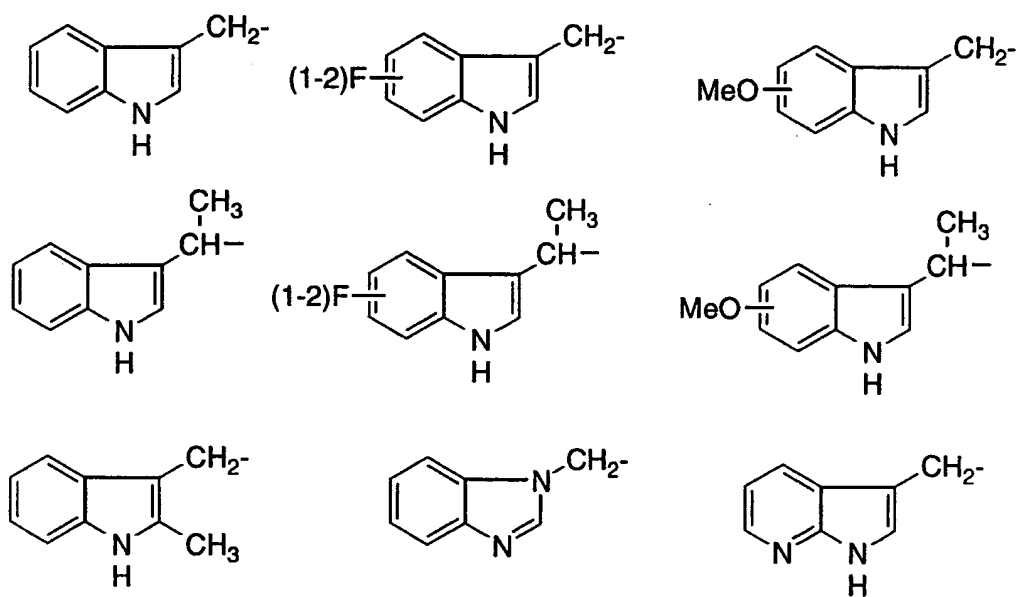


Formula Ib

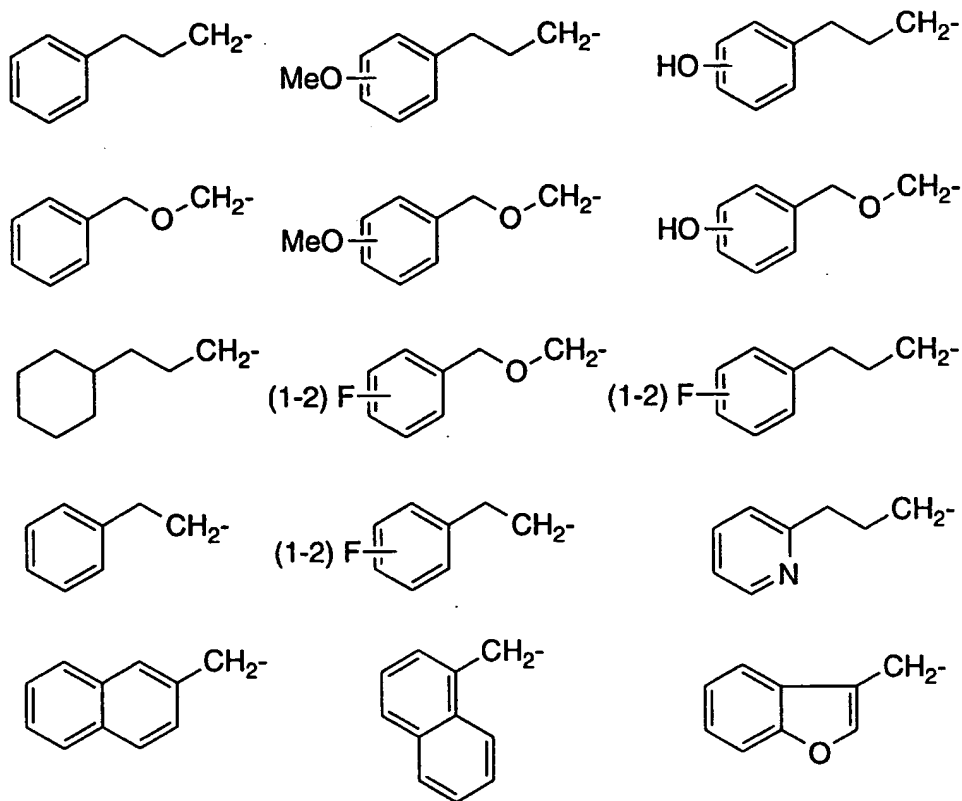
5

wherein:

R¹ is selected from the group consisting of:



- 105 -



or their regioisomers where not specified;

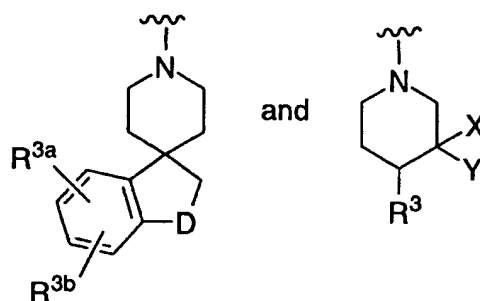
R^2 is selected from the group consisting of:

- 5 hydrogen, -C₁-C₆ alkyl, -C₃-C₇ cycloalkyl, and -CH₂-phenyl,
wherein the alkyl or the cycloalkyl is unsubstituted or substituted with
hydroxyl, C₁-C₃ alkoxy, thioalkyl, -C(O)OR^{2a}, and wherein, if two
-C₁-C₆ alkyl groups are present on one atom, the groups may be
optionally joined to form a C₃-C₈ cyclic ring being selected from the
- 10 group consisting of pyrrolidine, piperidine, piperazine, morpholine,
thiomorpholine;

R^{2a} is hydrogen, or C₁-C₄ alkyl;

- 106 -

B is selected from:

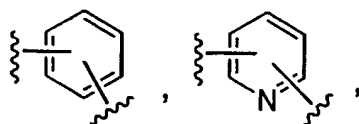


5 R^3 is selected from: hydrogen or phenyl, wherein the phenyl is substituted in the ortho position by a substituent selected from the group consisting of: C1-C6 alkyl, halogen, $-OR^2$, $-(CH_2)_rOR^6$, $-(CH_2)_rN(R^2)(R^6)$, $-(CH_2)_r(R^6)$, $-(CH_2)_rC(O)OR^2$, $-(CH_2)_rC(O)OR^6$, $-(CH_2)_rC(O)R^2$, $-(CH_2)_rC(O)R^6$, $-(CH_2)_rC(O)N(R^2)(R^2)$, $-(CH_2)_rC(O)N(R^2)(R^6)$, $-(CH_2)_rSO_2N(R^2)(R^6)$, $-(CH_2)_rSO_2N(R^2)(R^2)$, $-(CH_2)_rS(O)_mR^6$, and $-(CH_2)_rS(O)_mR^2$;

10

R^{3a} and R^{3b} are independently selected from: hydrogen, C1-C6 alkyl and halogen;

E is selected from: $-O-$, $-CH=CH-$,



15

which is optionally substituted with a substituent selected from: halo, hydroxy, $-N(R^2)(R^2)$, C1-C6 alkyl and C1-C6 alkoxy;

20 R^4 and R^5 are independently selected from hydrogen, C1-C6 alkyl, and substituted C1-C6 alkyl where the substituents are selected from halo, hydroxy, phenyl, and C1-C6 alkoxy carbonyl;

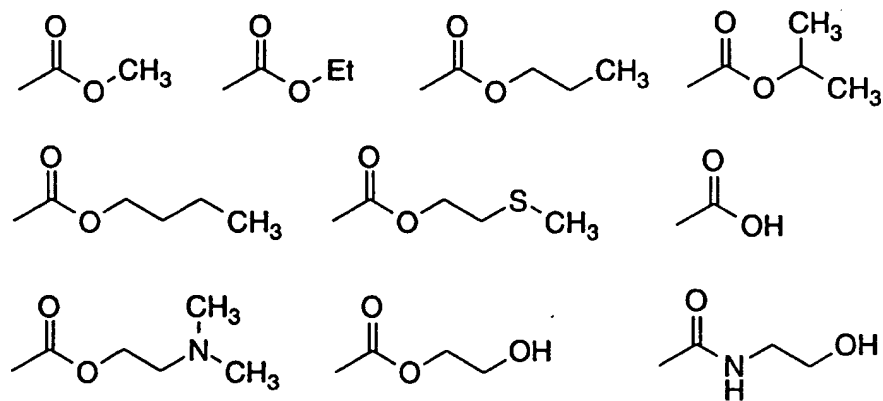
- 107 -

or R^5 and R^4 may be taken together to form $-(CH_2)_d-L_a(CH_2)_e-$ where L_a is $-C(R^2)_2-$, $-O-$, $-S(O)_m-$ or $-N(R^2)-$, d and e are independently 1 to 3 and R^2 is as defined above;

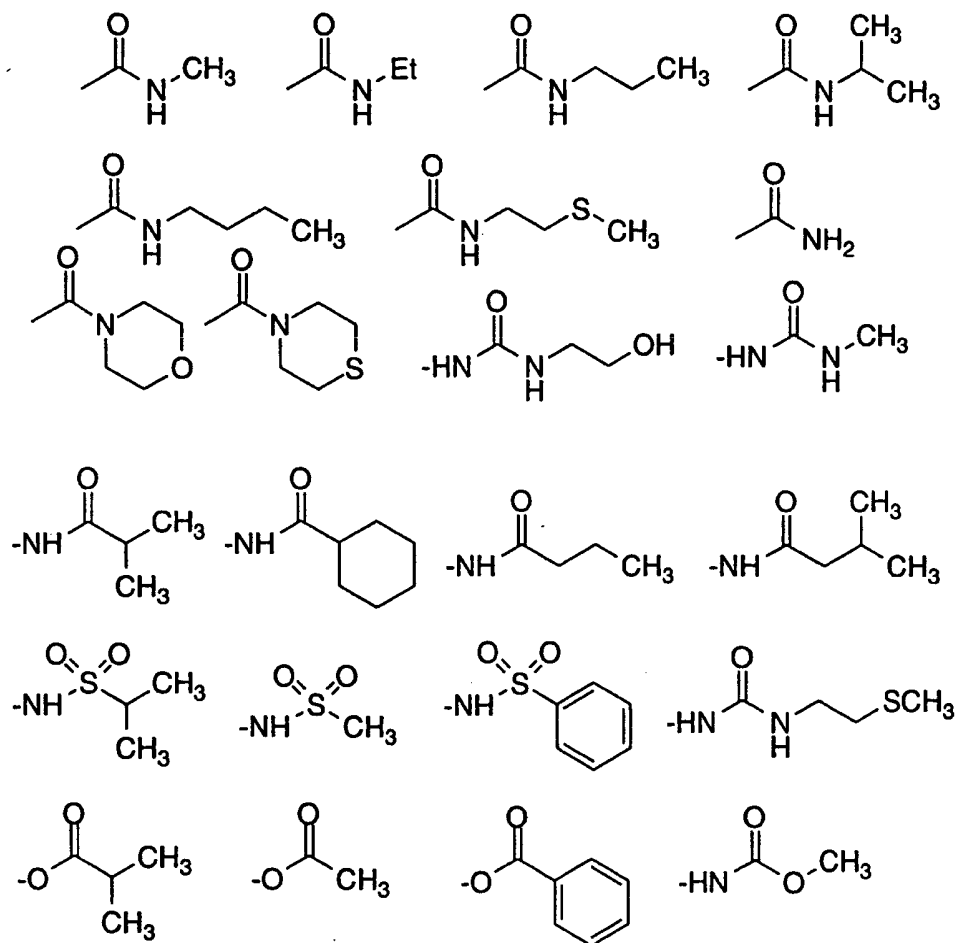
- 5 R^{4a} and R^{4b} are independently selected from: hydrogen, C_1 - C_6 alkyl, or substituted C_1 - C_6 alkyl where the substituents are selected from: imidazolyl, naphthyl, phenyl, indolyl, and p-hydroxyphenyl;

- R^6 is selected from: hydrogen, C_1 - C_6 alkyl, and $(CH_2)_v$ aryl, wherein
 10 the $(CH_2)_v$ and alkyl groups may be optionally substituted by $-O(R^2)$, $-S(O)_mR^2$, $-C(O)OR^2$, $-C(O)N(R^2)(R^2)$, $-SO_2N(R^2)(R^2)$, or $-N(R^2)C(O)N(R^2)(R^2)$, wherein the aryl group is selected from: phenyl, pyridyl, 1H-tetrazolyl, triazolyl, oxadiazolyl, pyrazolyl, thiadiazolyl, and benzimidazol-2-yl, which is optionally substituted with C_1 - C_6 alkyl, C_3 -
 15 C_6 cycloalkyl, amino, or hydroxyl;

X is selected from the group consisting of: hydrogen,

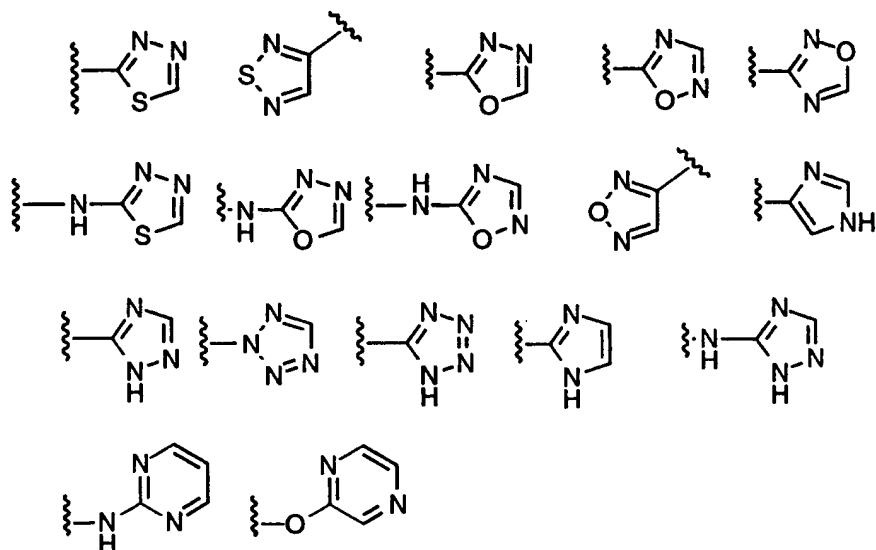


- 108 -



and further selected from the following group of heterocycles

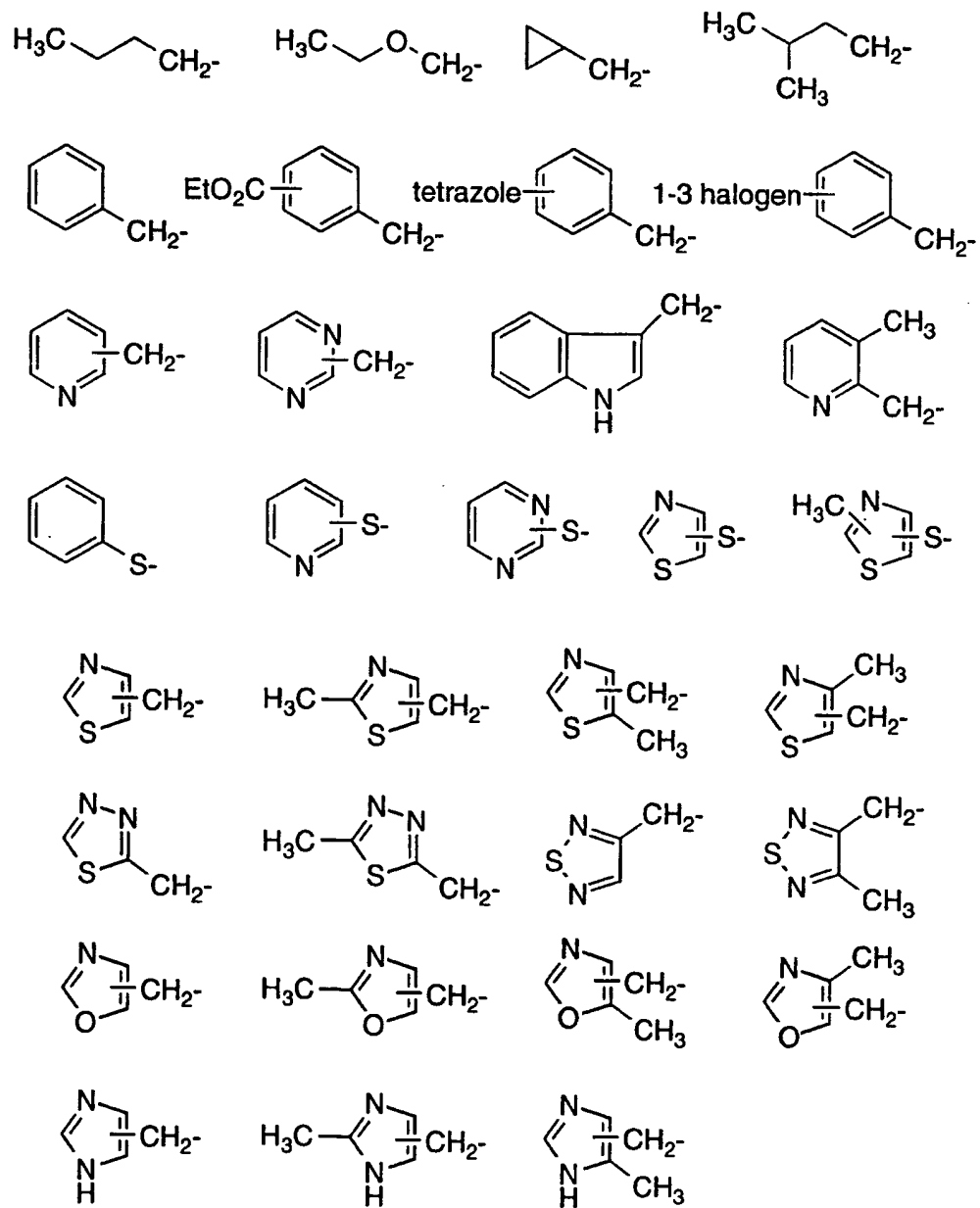
- 109 -



wherein the heterocycle is optionally substituted with a substituent selected from: $-N(R^2)(R^2)$, $-O(R^2)$, C_1 - C_3 alkyl, halogen, and trifluoromethyl;

- 110 -

Y is selected from the group consisting of: hydrogen,



5

or their regioisomers whereof where not specified;

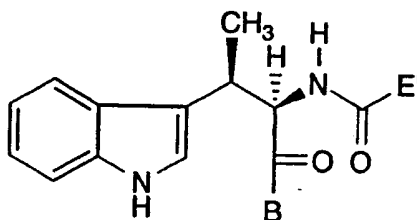
- 111 -

- D is selected from: $-N(R^7)-$, $-S(O)_m-$, $-C(O)-$ and $-C(H)(R^7)-$,
wherein R^7 is selected from: $-R^2$, $-(CH_2)_q\text{aryl}$, $-C(O)R^2$, $-SO_2R^2$, $-C(O)N(R^2)(R^2)$, $-C(O)OR^2$, 1-H-tetrazol-5-yl, $-SO_2N(R^2)\text{aryl}$, $-SO_2N(R^2)(R^2)$ and the $(CH_2)_q$ may be optionally substituted by C₁-C₄
5 alkyl, and the R^2 and aryl may be optionally further substituted with a substituent selected from: $-OR^{2a}$, $-C(O)OR^{2a}$, $-C(O)N(R^{2a})(R^{2a})$, halogen, C₁-C₄ alkyl, and the aryl is selected from triazolyl, oxadiazolyl, 1H-tetrazolyl, and thiadiazolyl;
- 10 1 is 0, 1 or 2;
m is 0, 1, or 2;
q is 0, 1, 2, 3, or 4;
r is 0, 1, 2, or 3;
t is 0, 1, 2, or 3;
15 v is 0, 1, or 2;
y is 1 or 2, with the proviso that if E is -O-, y is 2;

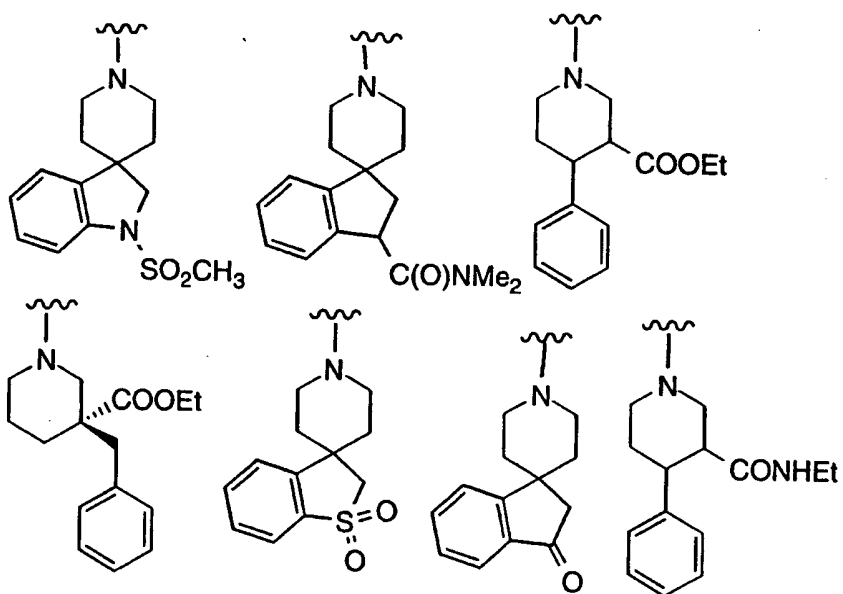
and pharmaceutically acceptable salts and individual diastereomers thereof.

- 112 -

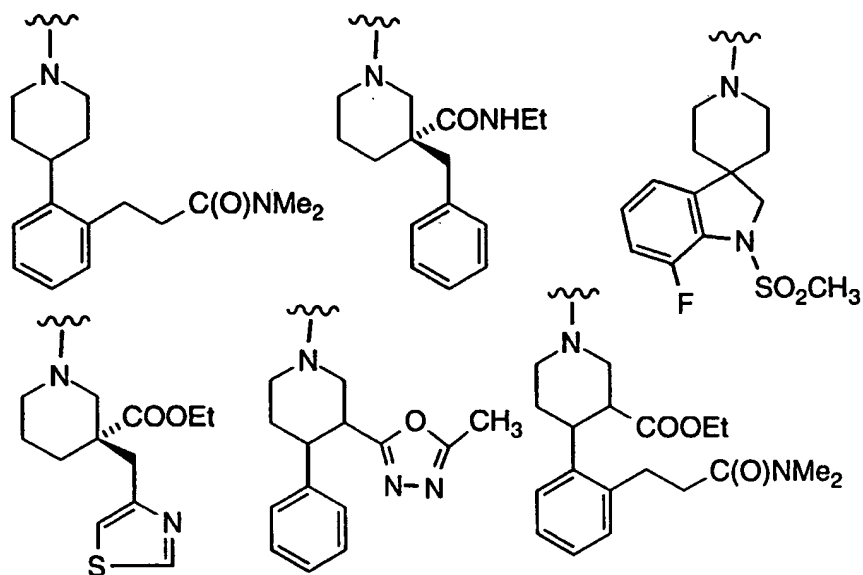
4. The compound of Claim 1 of the formula:



wherein B is selected from the group consisting of:



- 113 -



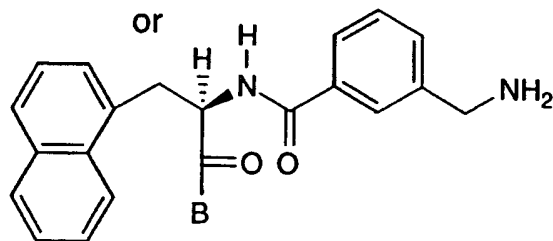
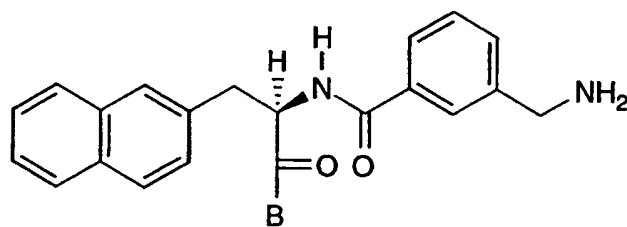
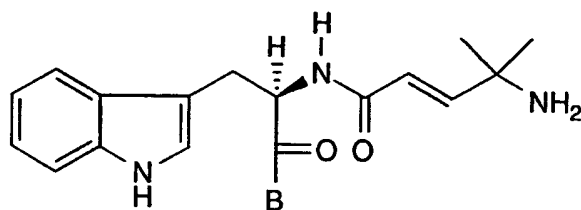
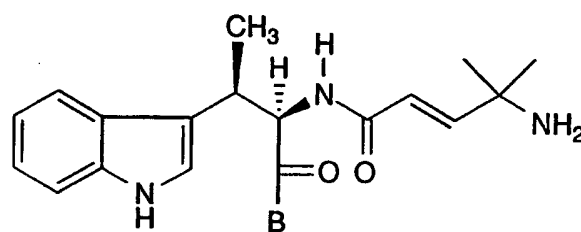
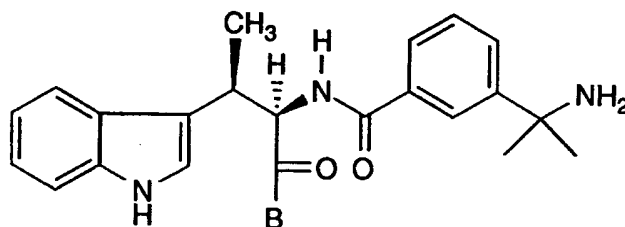
E' is selected from:

- 5 -CH=CH-CH₂-NH₂, -CH=CH-CH(CH₃)-NH₂,
 -CH=CH-C(CH₃)₂-NH₂,
 or phenyl substituted with -CH₂-NH₂, -CH(CH₃)-NH₂,
 or -C(CH₃)₂-NH₂;

and pharmaceutically acceptable salts and individual diastereomers thereof.

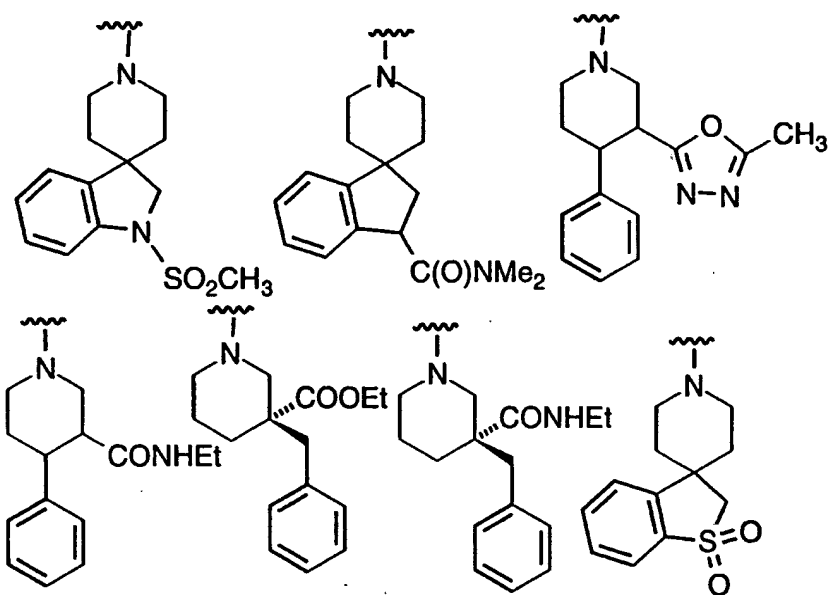
- 114 -

5. The compound of Claim 4 of the formula:



- 115 -

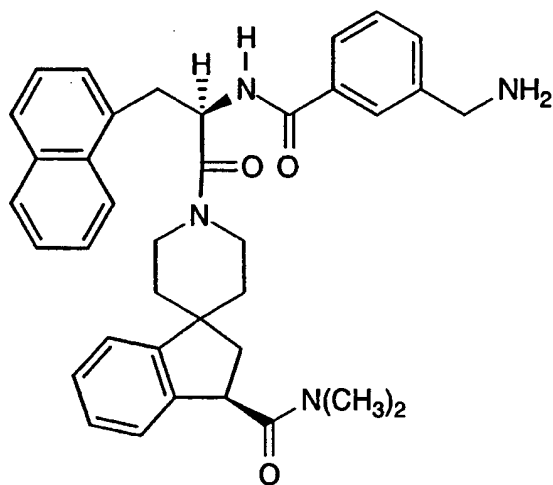
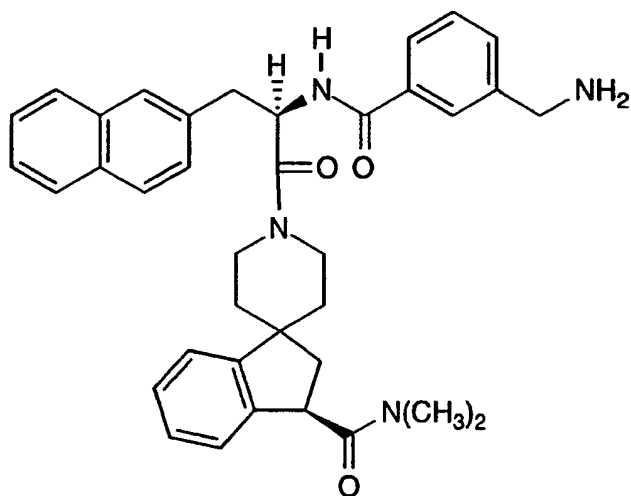
wherein B is selected from the group consisting of:



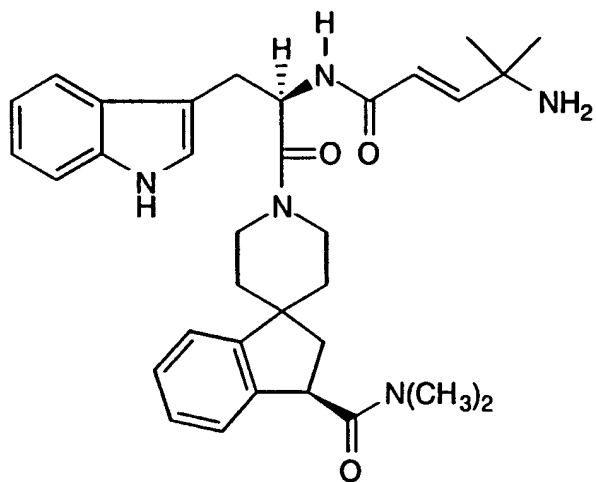
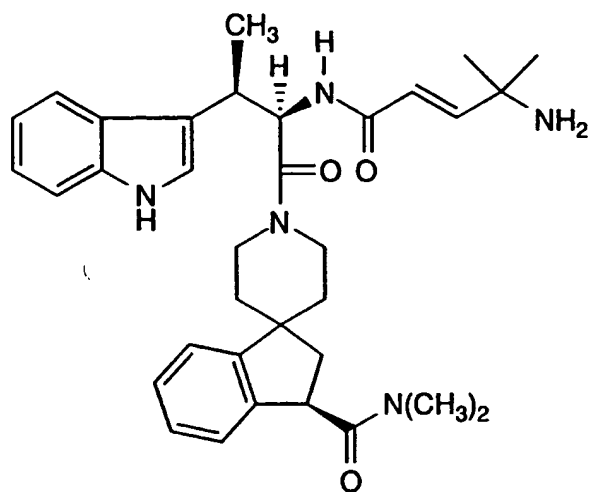
and pharmaceutically acceptable salts and individual diastereomers thereof.

- 116 -

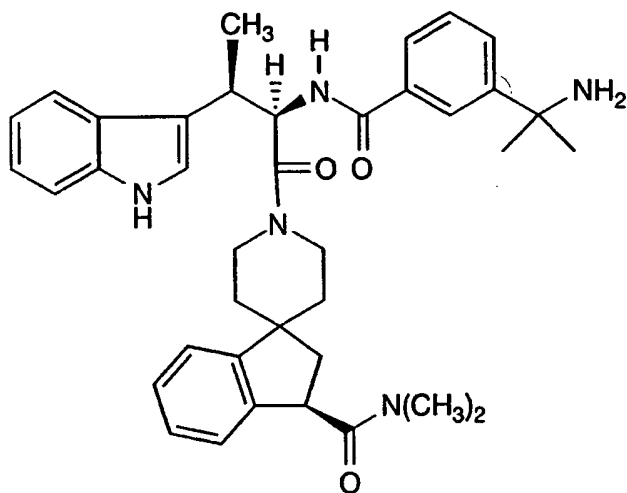
6. A compound which is selected from the group consisting of:



- 117 -



- 118 -



and pharmaceutically acceptable salts and individual diastereomers thereof where not otherwise specified.

- 119 -

7. A pharmaceutical composition which comprises an inert carrier and the compound of Claim 1.

5 8. A pharmaceutical composition useful for increasing the endogenous production or release of growth hormone in a human or an animal which comprises an inert carrier and an effective amount of the compound of Claim 1 in combination with an additional growth hormone secretagogue.

10 9. A pharmaceutical composition useful for the treatment of osteoporosis which comprises a combination of a bisphosphonate compound and the compound of Claim 1.

15 10. The pharmaceutical composition of Claim 9 wherein the bisphosphonate compound is alendronate.

20 11. A method for increasing levels of endogenous growth hormone in a human or an animal which comprises administering to such human or animal an effective amount of the compound of Claim 1.

25 12. A method for increasing levels of endogenous growth hormone in a human or an animal which comprises administering to such human or animal an effective amount of the compound of Claim 1 in combination with an additional growth hormone secretagogue.

30 13. The method of Claim 12 wherein the additional growth hormone secretagogue is selected from the group consisting of: growth hormone releasing factor; an analog of growth hormone releasing factor; IGF-1; and IGF-2.

14. A method for increasing feed efficiency, promoting growth, increasing milk production and improving the carcass quality of livestock which comprises administering to such livestock an effective amount of the compound of Claim 1.

- 120 -

15. A method for the treatment of a disease or a condition which is benefited by the anabolic effects of enhanced growth hormone levels that comprises administering to a patient in need thereof an effective amount the compound of Claim 1.

16. The method of Claim 15 wherein the disease or condition is selected from the group consisting of: osteoporosis; catabolic illness; immune deficiency, including that in individuals with a depressed T4/T8 cell ratio; bone fracture; musculoskeletal impairment in the elderly; growth hormone deficiency in adults or in children; short stature in children; obesity; sleep disorders; cachexia and protein loss due to chronic illness such as AIDS or cancer; and the treatment of patients recovering from major surgery, wounds or burns.

17. A method for the treatment of osteoporosis which comprises administering to a patient with osteoporosis a combination of a bisphosphonate compound and the compound of Claim 1.

18. The method of Claim 17 wherein the bisphosphonate compound is alendronate.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/16103

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) : Please See Extra Sheet.

US CL : Please See Extra Sheet.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : Please See Extra Sheet.

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

APS, CAS ONLINE, MEDLINE

search terms: growth(w)hormone, secret?, produc?, piperidin?

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	US 5,536,716 A (CHEN et al) 16 July 1996, see entire document.	1-18 ----- 1-18
X --- Y	US 5,492,920 A (CHEN et al) 20 February 1996, see entire document.	1-18 ----- 1-18



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:	*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
A document defining the general state of the art which is not considered to be of particular relevance	*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
E earlier document published on or after the international filing date	*Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*A* document member of the same patent family
O document referring to an oral disclosure, use, exhibition or other means	
P document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

04 NOVEMBER 1997

Date of mailing of the international search report

19 NOV 1997,

Name and mailing address of the ISA/US
Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231

Facsimile No. (703) 305-3230

Authorized officer

JANE C. OSWECKI

Telephone No. (703) 308-1235

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/16103

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☒ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
1-18
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US97/16103

A. CLASSIFICATION OF SUBJECT MATTER:

IPC (6):

A01N 43/08, 43/10, 43/26, 43/40, 43/74, 43/90; A61K 31/445; C07D 211/20, 211/26, 401/04, 401/12, 401/14, 405/04, 405/14, 409/14, 413/14, 417/14, 471/10

A. CLASSIFICATION OF SUBJECT MATTER:

US CL :

514/278, 318, 320, 321, 322, 323, 324, 326, 331, 333, 338, 339, 340, 342, 344, 357; 546/18, 193, 194, 196, 197, 198, 199, 201, 202, 205, 208, 209, 210, 211, 212, 213, 214, 215, 227, 228, 229, 230, 232, 237, 245

B. FIELDS SEARCHED

Minimum documentation searched

Classification System: U.S.

514/278, 318, 320, 321, 322, 323, 324, 326, 331, 333, 338, 339, 340, 342, 344, 357; 546/18, 193, 194, 196, 197, 198, 199, 201, 202, 205, 208, 209, 210, 211, 212, 213, 214, 215, 227, 228, 229, 230, 232, 237, 245

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING

This ISA found multiple inventions as follows:

Group I, claims 1 and 6, drawn to spiro compounds of Formula I and comprising a piperidine-containing spiro moiety as substituent B.

Group II, claims 1 and 6, drawn to non-spiro containing compounds of Formula I and comprising a piperidine moiety as substituent B.

Group III, claims 1 and 6, drawn to non-spiro containing compounds of Formula I and comprising a pyrrolidine moiety as substituent B.

Group IV, claims 1 and 6, drawn to non-spiro containing compounds of Formula I and comprising an azepine moiety as substituent B.

Claims 2-5 and 7-18 are generic to any group paid for.

The inventions listed as Groups I-IV do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: the special technical feature that distinguishes each group lies in the B substituent which is different in structure in each of the four groups and none of which are known as equivalents in the art.

THIS PAGE BLANK (USPTO)